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ENCEPHALOGRAPHY IN CASES OF INCREASED INTRA-CRANIAL PRESSURE *

W. James Gardner

Encephalography is an invaluable diagnostic procedure which until very recently has been used far too infrequently in the diagnosis of cerebral conditions. By the term encephalography is meant the spinal subarachnoid insufflation of air for the purpose of roentgenographic examination of the brain, as contrasted with ventriculography in which method the air is introduced directly into the lateral ventricles through trephine openings in the skull.

My experience with encephalography in cases of increased intracranial pressure would seem to indicate that the reluctance with which most neurological surgeons in the past resorted to this method was not entirely justified. During the past year in the Cleveland Clinic 24 encephalograms have been made in the cases of 19 patients in whom the spinal fluid pressures varied from 260 to 850 millimeters of water. Very few untoward symptoms have resulted from the procedure; as a matter of fact, it has been found that patients with brain tumor usually do not have as severe an immediate reaction to a spinal insufflation as do patients in whom other cerebral conditions are present.**

Encephalography should be resorted to in the diagnosis of cerebral conditions only after a careful history of the patient has been secured and a painstaking examination has been made. However, our experience would seem to indicate that in a very considerable number of cases in which a craniotomy is indicated an encephalogram should be made prior to operation. Few general surgeons will operate upon a kidney without a pyelogram having been made or upon a stomach without an x-ray examination of the gastro-intestinal tract. On the other hand, many patients with brain tumor have been subjected to an exploratory craniotomy with resultant negative findings, when a cerebral pneumogram would have more adequately localized the lesion. With the present refinements in technic, encephalography may be said to be com-

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**This lessened immediate reaction to encephalography in cases of brain tumor is probably due to the fact that as the cerebral sulci are obliterated by increased pressure, little or no air gains access to the sulci. Apparently it is the subarachnoid cortical air which in most cases causes the subjective complaints.

paratively safe, when the serious nature of the conditions which indicate its use is considered. Furthermore, by this procedure in many instances gross alterations in the cerebral structure may be diagnosed which can only be guessed at by any other method of examination, not excluding necropsy.

The technic of encephalography is very simple and therefore its application is much wider than that of ventriculography. At the Cleveland Clinic the procedure of encephalography is as follows: The patient is given a hypodermic injection of one grain of codeine and 1/150 grain of scopolamine one hour before the time set for operation. A preliminary spinal fluid pressure reading is made with the patient in the horizontal position after which he is placed in the encephalogram chair which is mounted on wheels. If the patient is cooperative, local anesthesia is used, but if a general anesthetic is indicated, avertin is preferred. The spinal puncture needle, after being introduced into the lumbar spinal canal with the patient in the sitting position is connected with two two-way stopcocks and a ten c.c. syringe which are placed end to end. A spinal manometer is connected to the side-arm of one stopcock, the side-arm of the other stopcock being used for the ejection of fluid from the syringe and for the aspiration of air. An initial pressure reading is then made with the patient in the sitting position following which five or ten c.c. of air is injected before any fluid is withdrawn. The fluid is withdrawn in five c.c. amounts and air is substituted in similar amounts until no more fluid can be obtained. The pressure reading is followed closely and is not allowed to fall below the original reading when the patient was in the horizontal position. If the pressure falls too rapidly more air is injected. If less than sixty c.c. of fluid is obtained and the patient complains of sub-occipital pain, an obstructive hydrocephalus should be suspected and the operator should hold himself in readiness to perform a ventricular tap in case of respiratory embarrassment.

During the insufflation of air, the patient's head is gently manipulated forward and backward and from side to side in order to insure a satisfactory emptying of the lateral ventricles. When the operation has been completed, roentgenograms are made with the patient still sitting in the encephalogram chair. If a view of the descending horns of the lateral ventricles is desired, further films should be made with the patient in the horizontal lateral position. This position is necessary in order to empty the descending horns which are dependent and therefore contain fluid when the patient is in the erect posture.

If the patient presents definite evidence of increased intra-cranial pressure the surgeon should be prepared to operate as soon

as the films are available, the reason for this being that the fluid tends to re-accumulate more rapidly after it has been once withdrawn. Thus if the pressure was high before the procedure, alarming symptoms may develop eight or twelve hours later unless a tumor is removed or a decompression provided. In the series of cases here reported no unfavorable postoperative symptoms were noted which could be traced to the previous air insufflation. One patient, who was not operated upon, died twelve hours after encephalography had been performed. Similar accidents, however, have followed ventriculography, ventricular estimation or even a simple spinal puncture. This patient, by the way, was critically ill before the procedure, and at necropsy was found to have an extensive encephalomalacia involving one entire hemisphere.

If an obstructive hydrocephalus is present, or if the brain is markedly distorted by a rapidly expanding hemispheric lesion, the ventricles may fail to empty properly. However, complete emptying of the ventricles has been observed in the case of obstructive hydrocephalus due to posterior fossa as well as to suprasellar tumors.

Failure to obtain satisfactory films by encephalography is probably not of more frequent occurrence than by ventriculography if the proper technic is observed. The preliminary injection of five or ten c.c. of air prior to the withdrawal of the fluid helps to insure satisfactory films and has not caused annoying symptoms. After the films have been obtained, the surgeon should correlate the roentgenographic findings with the clinical findings and should plan his operation accordingly.

The preliminary intravenous administration of concentrated glucose, or a ventricular tap, does not appear to be necessary either from the standpoint of safety to the patient or for the insuring of satisfactory films.

In analyzing the data in the accompanying table, it will be found that of sixteen cases of suspected brain tumor the lesion was correctly localized by encephalography in twelve instances, and in the remaining four cases the presence of a brain tumor was definitely excluded. Of the cases localized by the encephalography, cerebral hemispheric tumors were present in seven, a suprasellar cyst was present in one, and four were cases of posterior fossa lesions. In two of the last four cases a subsequent ventriculogram was performed in order to substantiate the findings from the encephalogram. In four cases a suspected brain tumor was definitely excluded by the encephalogram findings, the final diagnoses in these four instances being as follows: Spontaneous subarachnoid hemorrhage in one case, external hydrocephalus in two cases, and subdural

SUMMARY OF THE 19 REPORTED CASES

Case No.	Age and Sex	History	Positive Finding	Eye Examination	Skull X-ray	Spinal Pressure Horizontal Position
1 225924	25 yrs. Male	Generalized headache for 5 months. Diplopia 5 weeks. Unsteadiness and dizziness 1 month.	Negative	O.D.—3 D. O.S.—3 D. Visual acuity O.U.—6/6. Fields full.	Convolutional atrophy with atrophy of dorsum sellae.	650 mm.
2 234680	22 yrs. Female	Occasional headache and dizziness for 12 months. Weakness of right arm and leg with bilateral tinnitus for 6 months. Occasional vomiting for 3 months. Constant headache for three weeks.	Sluggish corneal reflexes. Deviation of tongue to left. Mild right hemiparesis with hyperreflexia. Bilateral Babinski, more marked on the right.	O.D.—1+D. O.S.—1+D. Visual acuity O.D.—6/6 O.S.—6/6. Fields show a slight contraction of the left superior quadrant in both eyes.	Dilated vessel grooves in left frontal region.	315 mm.
3 232621	39 yrs. Female	Headache for 7-8 years. Occasional convulsions for 1 year. Failing vision for 6 months. Vomiting and vertigo.	Mental torpor and irritability. Non-functioning left 8th nerve, both cochlear and vestibular. Bilateral Babinski.	O.D.—2 D. O.S.—2 D. Advanced secondary atrophy. Complete blindness.	Erosion of posterior clinoids.	470 mm. 10 c.c. removed 190 mm.
4 230060	30 yrs. Female	Headache for 3-4 years. Vomiting and failing vision for 2 weeks.	Obesity. Pupils react sluggishly to light. Left 3rd and 6th nerve weakness. Occasional rotary nystagmus.	O.D.—6 D. O.S.—4 D. Secondary optic atrophy. O.U.—counts fingers.	Negative	450 mm.
5 232232	45 yrs. Male	Generalized headache for 3 months. Stupor for 1 week.	Nystagmus, bilateral Babinski. Lower left facial palsy. Questionable left hemiparesis. Stupor.	O.D.—2 D. O.S.—2 D.	Negative	100 c.c. 50% glucose intravenously 400 mm.
6 233329	40 yrs. Male	Occasional right Jacksonian motor and sensory attacks with transient hemiparesis. Duration 5 months. Headache and vomiting for 1 month.	Negative	O.D.—1 D. O.S.—1 D. Visual acuity O.U. 6/5. Fields full.	Negative, calcified pineal not displaced.	270 mm.
7 234050	13 yrs. Male	Occasional headache and vomiting for 2 years. More frequent during past 3 months. Drowsiness and enlargement of head 4 months. Failing vision and diplopia 3 months. Staggering gait 1 month. Blindness for past week.	Sluggish mentality. Rather large head. Blindness, nystagmus. Absent corneal reflexes. Positive Romberg. Ataxia. Hyperactive patellars. Bilateral Babinski. Cracked pot sound on percussion of head.	O.D.—4½ D. O.S.—2½ D. Blind.	Marked separation of sutures.	550 mm.
8 231215	35 yrs. Male	Generalized headache, increasing in severity for past month. Completely irrational for past 48 hours.	B.P. 130/80. Temperature 101. Pulse 70. R. 20. Dehydrated. Stupor alternating with delirium. Stiff neck, positive Kernig and bilateral ankle clonus.	O.U. No choking of optic discs.	Negative	700 mm. Struggling. 10 c.c. removed 200 m.m.
9 227448	18 yrs. Male	Lack of physical and sexual development. Headache for past month.	Physical and sexual development of about 10 years.	O.U. Early choking. Visual acuity O.U.—6/10. Fields show bitemporal inferior quadrant loss for green.	Intrasellar calcification. Sella normal.	510 mm.

Encephalogram (Sitting Position) — Cases

Encephalogram (Sitting Position) — Cases

Case No.	Initial Pressure	Final Pressure	Fluid Removed	Air Injected	Anesthesia	Findings	Operation	Remarks
1 225924	?	?	80 c.c.	?	Local	No subarachnoid air. The anterior horns of the lateral ventricles are displaced to the right.	Left frontotemporal craniotomy with complete removal of frontotemporal meningioma.	Encephalogram performed in this case following introduction of a cannula into right ventricle.
2 236680	515 mm.	440 mm.	74 c.c.	82 c.c.	Avertin	No subarachnoid air. Air in posterior horns, none anterior.	Left frontal craniotomy with complete removal of midline chondroma arising from dura and sagittal sinus on left side.	A postoperative encephalogram showed dilated ventricles in about normal position.
3 232621	440 mm.	380 mm.	195 c.c.	205 c.c.	Local	No subarachnoid air. Uniform dilatation of lateral and third ventricles. Fourth ventricle not visualized.	Suboccipital craniectomy with complete removal of left acoustic tumor.	The history in this case was unreliable and the patient uncooperative in the neurological examination. Clinical diagnosis confirmed by encephalogram.
4 230060	520 mm.	?	27 c.c.	27 c.c.	Local	No subarachnoid air. Lateral ventricles displaced to left. Right ventricle compressed.	Large right temporal decompression.	Blood and spinal fluid.—Wassermann four plus. Colloidal Gold 111210000. Three cells. Diagnosis—right frontotemporal tumor or gumma.
5 232232	680 mm.	300 mm.	109 c.c.	118 c.c.	Local	Small amount of subarachnoid air over left hemisphere. None over the right. Left ventricle displaced to the left. Right ventricle not visualized.	Craniotomy with partial removal of right temporal lobe glioma. Decompression.	
6 233329	490 mm.	200 mm.	107 c.c.	115 c.c.	Local	No subarachnoid air. Slight displacement of ventricles to right. Roof of left ventricle d-pressed. Dilated third ventricle.	Left frontoparietal craniotomy with partial removal of glioma in left prerolandic area at vertex.	
7 234050	410 mm. following intravenous 50% glucose	350 mm.	220 c.c.	230 c.c.	Avertin	Enormous obstructive hydrocephalus with obliteration of third ventricle. Body of right ventricle pushed upwards and filling defect of body of right ventricle. No shift of midline structures. Some cortical air present.	Right frontoparietal craniotomy with evacuation of large gliomatous cyst and removal of large solid glioma which compressed the third ventricle.	Three weeks prior to encephalography an attempted ventricular tap disclosed a gliomatous cyst in the right parietal region containing 150 c.c. Ventriculogram and cystogram at this time showed the cyst with an obstructive hydrocephalus apparently due to compression of the third ventricle by a solid tumor. Death from pneumonia 2 weeks postoperatively.
8 231215	475 mm.	390 mm.	96 c.c.	90 c.c.	Avertin	No subarachnoid air. Left ventricle dilated and right very much compressed. Both displaced very markedly to left.	No operation.	Sudden death 12 hours after encephalogram due to respiratory paralysis. Necropsy disclosed encephalomalacia of the entire right cerebral hemisphere.
9 227448	660 mm.	450 mm.	42 c.c.	55 c.c.	Avertin	No subarachnoid air. Lateral ventricles greatly dilated as shown by the position of a small bubble of air in each. No air in third ventricle. Fourth ventricle and aqueduct visualized.	Right frontal craniotomy with complete removal of large suprasellar cyst.	Patient died 6 hours postoperative. In this case death was ascribed to operative trauma to the structure in the interpeduncular region. The pituitary stalk and tuber cinereum were lacerated during the removal of the cyst capsule.

SUMMARY OF THE 19 REPORTED CASES — Continued

Case No.	Initial Pressure	History	Positive Finding	Eye Examination	Skull X-ray	Spinal Pressure Horizontal Position
10 226915	19 yrs. Female	Obesity with increasing mental sluggishness for 5 years. Delayed and irregular menses with onset at 18 years.	Mental sluggishness, obesity with scanty pubic hair.	O.U.— Secondary optic atrophy. Visual acuity. O.U.—6/7.5. Fields contracted.	Pronounced convolutional atrophy.	260 mm.
11 226710	20 yrs. Female	Occasional headache for 2 years. Constant headache for 2 months with vomiting, failing vision and mild ataxia.	Mild right hemiparesis with ataxia. No nystagmus.	O.D.— 3 D. O.S.— 3+D. Visual acuity O.D.—6/7.5. O.S.—6/10. Fields full.	Negative	450 mm.
12 199065	37 yrs. Male	Headache for 5½ years. Bilateral tinnitus for 3 years. Vomiting and failing vision for 1 year.	Nystagmus. Absent corneal reflexes. Lower right facial paresis. Mild bilateral nerve deafness. Positive Romberg. Pharyngeal and palatal reflexes absent.	O.D.— 4 D. S.D. Visual acuity O.D.—6/7.5. O.S.—6/10. Fields show a concentric contraction.	Negative	310 mm.
13 225002	27 yrs. Male	Severe attack of quinsy 5 months ago. Occasional left Jacksonian attacks with bilateral tinnitus 2½ months.	Slight exaggeration of left patellar reflex. Complete deafness in left ear. Moderate nerve deafness in right. Vestibular responses absent on left.	O.D.— 2 D. O.S.— 1 D. Fields show a questionable right homonymous cutting.	Negative	290 mm.
14 233183	18 yrs. Female	Operation for cervical adenitis 9 months ago. Left parietal headache for 3½ months. Failing vision and diplopia for 2 weeks.	Operative scar right cervical region. Mild internal strabismus. Right ptosis congenital. Positive Romberg. Tenderness in left parieto-occipital region.	O.D.— S.D. O.S.— 4 D. Visual acuity O.D.—6/60. O.S.—6/30. Fields full.	Negative	2/15/30 700 mm. 2/24/30 850 mm. 4/2/30 850 mm.
15 232646	16 yrs. Male	Pansinusitis with septicemia 9 weeks previously. Right sided headache and left hemiparesis for 6 weeks.	Tenderness in right frontotemporal region. Left hemiplegia.	O.D.— 3 D. O.S.— 2 D. Vision well preserved. Questionable left homonymous hemianopsia.	Slight separation of sutures. Small area of osteomyelitis right frontotemporal.	410 mm. 15 c.c. removed 160 mm.
16 160860	25 yrs. Male	Paroxysmal excruciating headaches for 6 years. Failing vision for 2 months.	Negative	O.D.— 8 D. O.S.— 6 D. Numerous hemorrhages. Visual acuity O.D.—4/60. O.S.—1/60.	Negative	550 mm. 15 c.c. removed 180 mm.
17 228417	37 yrs. Male	General weakness. Protrusion of eyes and deafness in left ear for past 4 months.	Generalised adenopathies. Very marked exophthalmos of left eye. Moderate exophthalmos of right eye.	O.D.— 1+D. O.S.— 1+D. Visual acuity O.U.—5/5. Fields full.	Negative	450 mm. 13 c.c. removed 225 mm.
18 232398	42 yrs. Female	Headache increasing in frequency for past 8 months. Dizziness, diplopia and failing memory.	B.P. 130/70. Mild mental confusion. Left pupil larger than right. Babinski right.	O.D.— 1 D. O.S.— 1 D. Visual acuity O.D.—6/12. O.S.—6/10. Fields show right homonymous cutting.	Negative	310 mm.
19 229980	23 yrs. Male	Mild cranial trauma 14 months ago. Headache, vomiting and dizziness for 7 weeks. Loss of 38 pounds in weight. Failing vision.	Emaciated. Bilateral loss of sense of smell.	O.D.— 1 D. O.S.— 1 D. Fields full. Visual acuity O.U.—6/6.	Negative	360 mm.

Encephalogram (Sitting Position) — Cases

Encephalogram (Sitting Position) — Cases

Case No.	Initial Pressure	Final Pressure	Fluid Removed	Air Injected	Anesthesia	Findings	Operation	Remarks
10 226915	?	?	60 c.c.	60 c.c.	Local	Air between cerebral hemispheres and beneath tentorium. No air in ventricles.	Suboccipital craniectomy with attempt to relieve obstruction of aqueduct.	Encephalogram diagnosis of obstructive hydrocephalus verified by ventriculogram. 375 c.c. removed from ventricles. Patient died 48 hours after operation. Autopsy showed a congenital obstruction of aqueduct of Sylvius.
11 226710	700+ mm.	220 mm.	45 c.c.	45 c.c.	Local	Air obstructed at the foramen magnum.	Suboccipital craniectomy with evacuation of right cerebellar gliomatous cyst.	Encephalogram diagnosis obstructive hydrocephalus. Verified by ventriculogram.
12 19005	600 mm.	?	55 c.c.	55 c.c.	Local	Air blocked at the foramen magnum.	Suboccipital craniectomy disclosed chronic arachnitis.	Respiration ceased during administration of anesthetic for craniectomy. Reinstituted by ventricular tap.
13 225002	700 mm.	200 mm.	110 c.c.	100 c.c.	Local	Decreased amount of subarachnoid air. Ventricles displaced to left. Roof of right ventricle depressed.	Drainage of brain abscess of right vertex behind motor area. Streptococcus.	Encephalogram showed abscess to be situated posterior to previous exploration.
14 233183	?	?	2/15/30 100 c.c. 2/24/30 110 c.c. 4/2/30 110 c.c.	80 c.c. 90 c.c. 80 c.c.	Local Avertin Avertin	2/15/30—Very little subarachnoig, ... Ventricles displaced to rt. Compression of left posterior horn. Rt. ventricle larger than left. 2/4/30—Little change in picture. 4/2/30—Further displacement to the right.	2/11/30—Drainage of extradural abscess. 4/7/30—Parietal craniectomy with evacuation of very large extradural tb. abscess.	Culture of pus sterile. Spinal pressure remained high in spite of apparently adequate drainage. Encephalogram disclosed no evidence of abscess elsewhere. Complete recovery following radical evacuation of large amount of caseous material.
15 23204	700 mm.	?	92 c.c.	75 c.c.	Avertin	Fourth ventricle contained air but there was none above this point.	Drainage of right frontotemporal staphylococcic abscess 4-5 ounces.	Previous operation disclosed a small extradural abscess in frontal region. Enceph. performed because of suspected multiple abscesses. Films unsatisfactory.
16 160860	750 mm.	270 mm.	195 c.c.	185 c.c.	Avertin	Very pronounced increase in subarachnoid air. Very mild ventricular dilatation.	Right subtemporal decompression	No recurrence of headaches. Pressure entirely relieved Diagnosis—external hydrocephalus of unknown etiology
17 229417	590 mm.	200 mm.	146 c.c.	125 c.c.	Local	Ventricles normal. Left ventricle incompletely emptied. Marked increase in subarachnoid air.	Right subtemporal decompression.	Patient died 2½ months after operation with generalised lymphoid hyperplasia.
18 232398	625 mm.	240 mm.	74 c.c.	67 c.c.	Local	No subarachnoid air. Ventricular system normal.	Left subtemporal decompression.	Spinal fluid was definitely bloody. Blood and spinal fluid Wassermann negative. Diagnosis — spontaneous subarachnoid hemorrhage.
19 229980	550 mm.	?	120 c.c.	120 c.c.	Local	Subarachnoid air normal. Very mild ventricular dilatation. Otherwise normal.	Right subtemporal decompression with evacuation of large serous subdural effusion.	As the intracranial pressure was not relieved following the first operation, two subsequent encephalograms were performed which disclosed no evidence of tumor. A left subtemporal decompression was also performed. At present the intracranial pressure is entirely relieved and the patient is well on the road to recovery.

effusion in one case. Of three cases of brain abscess, the lesion was correctly localized in two and in the third case the lateral ventricles failed to fill.

Of the nineteen cases here reported, fourteen patients are living at the present time and in the case of nine of these fourteen the cure is apparently complete. Patient No. 17 died of a systemic condition four months after a right subtemporal decompression had been done. Patient No. 10 died seven days after encephalography, 48 hours after a ventriculogram had been made and a suboccipital craniectomy performed which failed to relieve a congenital stricture of the aqueduct of Sylvius. Patient No. 7 died of pneumonia two weeks after the evacuation of a large gliomatous cyst containing 150 c.c. and the removal of a large solid glioma which was pressing upon and obstructing the third ventricle. Patient No. 9 died with symptoms of a vasomotor collapse six hours after the complete extirpation of a large suprasellar cyst. Patient No. 8 died of respiratory failure twelve hours after encephalography, and necropsy in this case disclosed extensive encephalomalacia.

In some of the above cases an encephalogram was not necessary for the localization of the tumor; however, the films gave added proof that a tumor was present, so that if it were not found on the cortex, the operator could feel more justified in making a subcortical search.

SUMMARY

In appears that encephalography is a safe procedure in cases of increased intracranial pressure provided the surgeon is prepared to operate immediately after the findings from the encephalogram have been obtained. The autopsy table has shown that no one is infallible in cerebral localization and the neurological surgeon who spurns such laboratory aids as cerebral pneumography must pay the price in a higher percentage of negative explorations.

CLINICAL ASPECTS OF THE CANCER PROBLEM

GEORGE CRILE

It is not my purpose at this time to discuss the laboratory studies of cancer nor to make any references to the enormous literature on different phases of this vast subject, but rather to draw certain conclusions from the experience of my associates and myself in the treatment of 7,005 cases of cancer.

It is obvious that no one general rule of treatment, whether by surgery, irradiation or both can apply equally to malignant tumors of the different organs and tissues. Two general rules may, however, be stated and should be emphasized: (1) when possible every pre-cancerous lesion should be removed; and (2) an established cancer should be removed radically if it is operable; if inoperable then palliative surgery or radiation or both should be applied.

From the mass of investigations into the cause and treatment of cancer no other safe method of dealing with a cancer has as yet evolved. From all of these studies which have included the incidence of cancer in relation to race, climate, age and the bodily tissues, method of growth, the effects of various physical and chemical agents, we have learned one sure fact, namely, that cancer, whether of the external and visible parts or of the internal, invisible organs, obeys one general law of growth, and the old dictum based entirely upon clinical experience is established more uniformly than ever — namely, that the one and only cure for cancer is its early and complete removal. It is probable that with extending knowledge of the operation of physical laws in biological processes, new light may be thrown upon the causation of malignant growths, and that from this knowledge new methods of cure may be evolved. Already, investigations have shown that the electric capacity and conductivity of cancer of any part far exceeds the capacity and conductivity of the normal tissue, while the potential in cancer is opposite to that in normal tissue. The histologic appearance of a cancer offers a static picture of the cells. The capacity and potential measurements present the dynamic status of the cells, and it is with the dynamic status of the cells that we are primarily concerned in interpreting the status of any malignant or pre-malignant condition.

Whatever these and other investigations may disclose in the future it is true that at present we must be guided by clinical experience and it is in order that these personal experiences of my

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associates and myself may be evaluated with those of other reporters that this paper is offered.

Before proceeding to a discussion of cancer of the different organs and tissues, a statement regarding precancerous lesions should be included here. To my knowledge no cancer of the skin has ever grown upon a normal uninjured surface. Cancers of the skin are always located where there have been tumors, scars, moles, warts, keratoses or some form of irritation. The precancer stage may be a long one — a story of little scales picked off as often as they appeared; of a wart frequently irritated; of a neglected ulcer; of occupational irritation, etc.

Rarely, if ever, does cancer of the mouth occur in a perfectly sanitary mouth with normal teeth. There is always present an irritation from a ragged tooth, from leukoplakia, a fissure or a wart.

So, too, we know of few cancers of the gall-bladder without gallstone irritation; few or no cancers of the kidneys without stone irritation. In the intestinal tract cancer selects irritated areas such as the esophagus, the pylorus, the splenic flexure, the rectum.

We may conclude, therefore, that, in general, a precancer stage usually if not always exists and that in most instances the precancerous condition is remediable. Yet in spite of this fact, even in the visible precancerous conditions, how frequently do the physician and the patient supinely and irresolutely wait for disaster.

If every chronic irritation were removed; every chronic ulcer, wherever located, healed or excised; if every wart and mole were removed and every keratosis cured; if the mouth were kept wholesome and the teeth smooth; if unhealthy scar tissue were always removed and if needed the surface covered by skin grafting, then the problem of cancer of the skin and the mouth could be measurably, if not completely, solved.

The precancer conditions in the internal organs are in many instances no less amenable to treatment; the syphilitic ulcer or the papilloma which induces cancer of the larynx; the chronic ulcer of the stomach; the irritating stones and chronic inflammations of the gallbladder; the ulcers and chronic irritations of the large intestine and the rectum; the stones in the pelvis of the kidney; the benign tumor or inflammation of the breast; and so on through the long list of sources of irritation.

In view of this potency of the precancerous lesion the dictum that every precancerous lesion should be removed when removal is possible is secure.

The Skin: Radium appears to be the most efficient method for the treatment of cancer of the skin and subcutaneous tissues according to our experience with 597 cases with one exception — a pigmented mole should always be excised.

Cancer of the Buccal Surfaces: A study of 4500 reported autopsies performed in patients who had died from cancer of the head and neck made for me some years ago by Dr. L. W. Hitchings showed that in less than one per cent were secondary cancer foci found in distant organs and tissues. This localization of the cancer is due to the protection afforded by the collar of lymphatics of the neck, every portion of which is readily accessible. As far as metastatic dissemination is concerned cancer of the head and neck presents a far more favorable outlook than does cancer of the breast, the lymph channels from which lead to thoracic and abdominal metastases, or cancer of the stomach or intestines with its inaccessible retroperitoneal and liver metastases.

Above this lymphatic barrier metastases may take place rapidly, although cancer of each part of the head seems to follow a law of its own. Thus, cancers of the skin, of the mucous membrane of the cheeks, of the mucous membrane of the edge of the jaw, usually do not metastasize; cancers of the lip almost uniformly metastasize to the lymphatic glands under the jaw; cancer of the floor of the mouth usually metastasizes in the glands of the same side. Paired organs or distinctly one-sided foci usually metastasize regularly; while unpaired organs, as the tongue, or mesial tissue, such as the middle of the lip, metastasize irregularly and widely. For example: a marginal cancer of one side of the tongue may metastasize to the glands of the opposite side, usually low down toward the clavicle, although the metastasis may occur at any site, high or low, on the right or the left side.

Early cancers of the buccal surfaces are usually treated by radium but once they've advanced to the stage where lymphatic invasion is possible not only should the primary focus be removed but a block dissection of the regional lymphatics should be done also. The local excision of the primary focus alone is as illogical as the excision of a cancer of the breast without the removal of the regional glands. Next in importance to the block regional excision is the minimum handling of the carcinomatous tissue to avoid the possibility of the implantation of cancer cells in the operative field. In certain cases cauterization is the method of choice for the removal of the primary focus. Thus cancer within the mouth may be destroyed completely and more easily by the cautery than by surgical operation. In the choice of method, however, it should be borne in mind that surgery

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produces the best scars, and when the cancer is in the cheek or well back in the jaw the cautery may produce a badly contracting scar and a plastic operation in a postoperative cancer field is to be avoided. Moreover, the cautery does not provide for the removal of a "platter" of underlying bone as is advisable in cases of cancer of the buccal mucous membranes.

It should be emphasized that while radiation of the local lesion may be indicated, radiation of the involved lymphatic glands of the neck should not be done, as this treatment cannot be depended upon. If the glands of the neck have been irradiated and the patient has recovered, we must conclude that the glands of the neck probably were not involved. After operation on any part of this field, postoperative treatment with deep, accurately measured x-ray or radium radiation is of advantage.

Our series includes 564 cases of cancer of the buccal surfaces among which there were 259 cases of cancer of the lip, and 128 cases of cancer of the tongue.

The Antrum: In the treatment of cancer of the antrum, of which our series includes 30 cases, any method which destroys the tumor is of value as it is enclosed in a bony box. Treatment with radium is, therefore, eminently successful although the application of diathermy and the electrocautery may be followed by good results. Whatever method for the removal of the tumor itself is employed a wide open surface wound is necessary, a point which has been emphasized by Dr. T. E. Jones, as this makes it possible to see and treat any recurrences as soon as they develop.

The Larynx: In view of the strategic position and importance of the larynx in its relation to the respiratory tract, it is not surprising that the encroachment upon or within it of a malignant growth should be viewed by the layman with peculiar and almost hopeless dread, or that the successful removal of the larynx should be one of the later achievements of surgery. Yet the complete extirpation of an intrinsic cancer of the larynx is one of the most successful operations for cancer as far as the ultimate cure of the cancer is concerned, and the comparative safety of the laryngectomy itself is attested by the fact that in my own series of cases the mortality rate compares favorably with that of excisions of the tongue or of the rectum for cancer.

The ultimate cure of a given case of cancer of the larynx depends principally upon whether it is primary or secondary; and if primary, whether it is intrinsic or extrinsic. If secondary, the cancer is an extension through the lymph channels from the tongue, throat or

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some other part of the head or neck, and it is obvious that, in such a case, the removal of the larynx would almost inevitably be futile.

Extrinsic cancer of the larynx, as the term implies, has its origin in some part or parts outside the larynx proper, such as the epiglottis or the arytenoids. Because of the abundance of lymphatic connections, this form of laryngeal cancer extends rapidly and is quickly fatal, and operation for its relief is at best but a desperate palliative remedy.

Intrinsic laryngeal cancer, on the other hand, starts within the larynx itself, in the vocal cords, the ventricular bands or the parts below. Since the walls of the larynx consist of hyaline cartilage, and cancer can rarely penetrate cartilage, intrinsic cancer of the larynx is contained as it were in a safety deposit box. Its only avenues of egress are through the thyro-hyoidean membrane, through mucous membrane invasion upward, and to a very limited extent through the sparsely supplied lymphatics. Because of the early involvement of the vocal cords, the presence of the cancer is early made known by every spoken word and there is a persistent hoarseness which promptly leads the patient to seek relief. Not every instance of chronic hoarseness, however, is due to cancer.

In extrinsic cancer of the larynx the only hope lies in the local removal of the growth and a block dissection of the gland-bearing area. In inoperable cases in which only tracheotomy can be attempted radium is of value as a palliative measure.

For intrinsic cancer of the larynx, laryngectomy is indicated. If the cancer is entirely intrinsic, laryngectomy offers a practical certainty of cure. Radium, therefore, is not indicated but the postoperative application of the x-ray may be of value as it may check any extension of the growth for there may be some undiscovered extrinsic focus or some cancer cells may become imbedded in the course of the operation.

Our series includes 159 cases of cancer of the larynx, in 74 of which laryngectomy was performed. Among the patients regarding whom we have later data, seven have survived for more than five years; of these seven patients, one has lived 17 years and one 31 years.

The Thyroid Gland: In our total series of 16,770 thyroidectomies there has been a malignant tumor in 265 cases. In about 90 per cent of these cases malignancy was due to the degeneration of an adenoma. For this reason I believe that all adenomata should be removed. Treatment of malignant tumors of the thyroid gland is thus mainly a problem of prevention. Once malignant changes have taken place in the gland, it should be removed surgically if

possible; otherwise, it should be treated with x-rays. If the malignant process has developed to the inoperable stage, a decompression operation will give temporary relief from obstruction and the resultant partial asphyxiation, and this operation should be followed by radiation.

It has been estimated that in the average case of inoperable carcinoma of the thyroid the patient will live without radiation for approximately a year. There is, at present, no basis upon which to found a judgment as to the average length of life when such a case is treated with radiation. In all cases of malignant disease of the thyroid, however treated, the possibility that myxedema may develop should be borne in mind. This condition, however, is readily corrected by the administration of thyroid extract.

Sometimes, as the result of radiation, the carcinoma will disappear; in other cases radiation seems to be of no avail. What the end-result of decompression and radiation may be in any given case cannot be foretold, but the patient is certain to have a period of relief. It must be borne in mind that involvement of the neighboring tissues is almost sure to be present, and that if the cancer involves the trachea there is practically no hope of cure.

The Breast: The one important point to bear in mind in the consideration of any tumor of the breast is that it may be the starting point of a malignant growth. This is true whatever etiological factors may seem to have been involved in the formation of the tumor; whatever its site, whatever the age of the patient, whatever the family history may disclose. There are certain lesions of the breast, however, which may safely be omitted from this generalization; simple cysts, lipomata, traumatic fat necrosis, hypertrophy, acute mastitis, mastitis neonatorum, mastitis adolescentium, echinococcus cyst, and syphilis.

Chronic mastitis deserves special consideration because of the diversity of opinion as to its cancerous potentialities. In general it is acknowledged that a lesion of this type may become malignant, especially if the lesion is unilateral. If the condition is present in both breasts malignant changes almost never develop.

In regard to the so-called benign tumors, Deaver has stated, "Tumors of certain types having certain structure are constantly harmless; those of other types, having another structure, are persistently invasive, destructive and constantly fatal. Unfortunately these are the extremes of a series between which lie many tumors that may or may not be harmful, or whose structures may fail to give a clue to their true disposition." I am far from recommending the radical operation in every case of tumor of the breast, but I do

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wish to emphasize the importance of frequent examination of the breast after the local excision of what appears to be a benign tumor, so that the radical operation may be performed immediately if the lesion shows any suspicion of malignancy. A biopsy should never be performed, for if the growth should prove to be malignant there is danger of its dissemination, and whatever its character, in any case it should be removed entirely and then sectioned.

Since the potentially precancerous lesion may be treated by simple excision, while once malignancy has been established the regional glands must be removed also, the problem for the surgeon is the accurate differentiation between benign and malignant tumors. Frank cancer is easily diagnosed, but the diagnosis of border-line cases is by no means a simple problem. Bloodgood at one time submitted specimens from over sixty border-line cases to a number of pathologists. These pathologists were divided into two groups, one of which favored a diagnosis of cancer, the other believed the growth to be a benign lesion. "In not a single case has there been a uniform agreement as to whether the lesion was benign or malignant."

Ewing states that "the great majority of mammary cancers are rather easily recognizable by inspection and palpation." In cases in which the clinical symptoms and the frozen section cannot give absolute proof of the character of the tumor, the utmost safety of the patient demands the complete excision of the breast and of the regional lymphatics, for unlike cancer of the head and neck or the imprisoned, intrinsic cancer of the larynx, the abundant, lymphatic channels from the breast may readily and easily produce thoracic and abdominal metastases.

There has been a great deal of discussion during recent years regarding the relative values of radium combined with deep x-ray therapy and of radical operation in the treatment of breast carcinoma. These discussions have centered about three phases of the problem: (1) the value of preoperative radiation; (2) the value of postoperative radiation; (3) radiation in preference to surgery.

From a study of the end-results in our own series, Portmann draws the following conclusions:

"1. Intensive x-ray therapy, especially by the cross-fire method, is not the preferred procedure for the postoperative treatment of carcinoma of the breast.

"2. Postoperative x-ray therapy by moderate repeated dosage decreases the number of recurrences and metastases, and prolongs the lives of many patients suffering from carcinoma of the breast."

We, therefore, give radiation therapy as soon as possible after operation, not waiting until the wound is healed. Only if a case is

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entirely inoperable is radiation employed as a palliative measure instead of surgery.

Our series includes 1522 cases of cancer of the breast.

Esophagus: Cancer of the esophagus, of which we have seen 147 cases, is one of the most hopeless among malignant conditions, as the disease is usually well developed when diagnosed and the progress of the disease is always exceedingly rapid. Thus, in a study of 31 of our cases of carcinoma of the esophagus, the duration of symptoms had been less than 10 months in all but 5 cases, less than 6 months in 18, less than 3 months in 11, less than 1 month in 6, and yet in many of these cases emaciation and exhaustion as a result of dysphagia were already marked.

Cancer of the esophagus is one of the hopeless types of malignancy as the disease is usually well developed when diagnosed. The surgical removal of the tumor is an exceedingly formidable operation and is hardly justified, the best treatment being the application of radium through an esophagostomy, and this does little good. Deep x-ray therapy is not applicable to these cases, as radiation may produce fibrosis of the lung.

Stomach: As in the case of cancer of the esophagus, a cancer of the stomach is characterized by a rapidity of growth, and an extent of lymphatic involvement so that the "dead line" of inoperability is reached very early in its progress. A period of a few weeks may be sufficient to carry the patient from an operable to a completely inoperable condition and consequently in the majority of cases the patient comes to operation too late for possible cure. A study of the records of our 713 cases of cancer of the stomach shows that the history is commonly a history of vague initial symptoms of indigestion or ulcer; that ulcer of the stomach has a moderate potentiality as a precancerous condition; that the history and the x-ray findings coupled with the effects of ulcer management on the size of the mass as revealed by repeated x-ray examinations are the most valuable means of diagnosis; that a differential diagnosis between an old ulcer and early cancer cannot be made with certainty; that when the probability of cancer is suspected an exploration should be made at once. In late cases, as in late cases of cancer elsewhere, even though the operation is survived and the local lesion removed, there is great danger of metastases, especially in the liver or retroperitoneal glands.

When operable, as in the case of cancer elsewhere, resection with the widest possible excision of the growth is the indicated procedure. Blood transfusion, saline infusions, nitrous oxide analgesia, the application of hot packs and divided operation may

suffice, however, to carry through many patients in whom the prognosis appears to be hopeless, but in whom the anatomical possibilities of operations have not been passed.

Radiation cannot be applied in these cases because it is impossible to deliver sufficient radiation to the stomach to destroy a malignant process without harming the adrenals, liver, pancreas, etc.

Gallbladder: Carcinoma of the gallbladder is usually associated with cholecystitis and consequently in most cases the disease has extended into the liver and adjacent deep structures before the malignant condition is recognized, and it is then too late for any operation to be of avail. For this reason the prognosis is extremely unfavorable even after a radical operation. However, if the presence of the malignant condition is recognized before extension to the liver has occurred an immediate cholecystectomy is indicated.

Our records include 67 cases of cancer of the gall-bladder and bile ducts.

Intestines and Rectum: The diagnosis of carcinoma of the small intestine is made from the history and clinical signs and the x-ray picture. If the presence of a cancer is indicated then an exploratory operation should be performed to determine operability, with immediate removal of the growth if possible. As in the case of carcinoma of the stomach, every available method for the conservation and restoration of the patient should be employed. Our records include 25 cases of carcinoma of the small intestine.

As for cancer of the large intestine and rectum of which we have seen 819 cases, the following points summarize the present status of opinion regarding its treatment: carcinoma of the large intestine tends to remain local; wide excision of the cancer should be made — the excision including the related lymphatic glands; the cancer tissue should be handled lightly; in cases of acute obstruction a colostomy should be performed first and the resection deferred; postoperative radiation probably contributes to cure; the treatment of cancer of the cecum and of the ascending colon is more successful than that of cancer in any other portion of the large intestine.

It should never be forgotten that cancer of the large intestine, like cancer anywhere else, may spread by three routes: (a) by direct extension through tissue, (b) through the venous system, (c) through the lymphatic system. In cases of carcinoma of the large intestine and rectum, a colostomy should be performed, followed by radical operation, x-ray radiation being employed after the operation. In cases in which the growth is so low in the rectum

as to be readily accessible, the implantation of radium needles and the application of radium packs may be sufficient. In inoperable cases a colostomy should be done, followed by radiation. There should be a period of about ten days between the colostomy and the final operation, or rather, between colostomy and the decision as to the method of treatment, as a period of that length of time is necessary to allow the inflammatory reactions of the disease to subside sufficiently to make it possible to determine what operation shall be performed. This decision depends, of course, upon the findings of an exploratory operation. The entire picture may change during this period.

While the application of deep x-ray radiation is beneficial after operation or after radium treatment, it is of little, if any, value in the treatment of recurrences.

A statistical study of our cases made recently by Dr. T. E. Jones shows that after resection and radiation 20.6 per cent of the patients survived for more than five years, while this survival period was reached in only 7.2 and 7.4 per cent respectively of the cases in which resection alone or radiation alone was employed. These figures show, however, as Jones has reported, that although operation by the abdominoperineal route, combined with radiation, yields the best end-results with a primary mortality of 10 per cent, if operation is refused or if the condition is inoperable, there is sufficient evidence that a cure can be obtained in certain cases and marked palliation in others by the use of radium and roentgen ray.

Genito-urinary organs: In general, reliance must still be placed upon surgery for the treatment of carcinoma of the genito-urinary organs. In some cases carcinoma of the kidneys in children will be reduced by deep x-ray therapy, but the radiation must be followed later by surgery. In the case of deep-seated bladder tumors, radium has seemed to prevail in certain cases, but here also the results are still too uncertain for radiation to be used routinely. Postoperative radiation is employed in many cases, but more because it is hoped that it may be of avail than because of any definite results. For malignant tumors of the kidneys in adults the indicated treatment is surgery with radiation both before and after operation. In many cases radiation will so reduce the size of the tumor that cases which have seemed to be inoperable become operable. Tumors of the kidney should be irradiated no matter how hopeless their outlook. In the case of deep-seated bladder tumors, radium has seemed to prevail in certain cases, but the results are too uncertain for radiation to be used routinely. Postoperative radiation is employed in many cases, but principally because of the hope that it

may be of avail rather than because of any definite results that have been secured up to the present time.

Malignant tumors of the testes are treated by surgery with radiation both before and after operation.

Whether or not prostatectomy or radiation is the preferred treatment for carcinoma of the prostate remains to be decided. According to the belief of Dr. Lower prostatectomy is to be preferred in uncomplicated cases, but in cases in which a high blood urea cannot be reduced, radiation may provide the only possible method of treatment, or it may tide the patient over until prostatectomy can be performed. Dr. Lower's series includes 316 cases of cancer of the prostate, 379 cases of cancer of the urinary bladder, and 39 cases of cancer of the kidney and ureter.

Uterus: The preferred treatment of carcinoma of the fundus still seems to be *sub judice* both as to whether surgery or radiation is the treatment of choice, and as to the type of operation to be performed. The end-results of surgery and of radiation are approximately the same. It would seem, however, that since surgery in combination with the postoperative employment of radium and x-ray gives the assurance of saving a large majority of the patients who present themselves in the operative stage, and of palliating suffering and prolonging the life with a fair prospect of ultimate cure in doubtful cases, we should hesitate to abandon such certainties for the uncertainties still presented by the use of radium and the x-ray without surgery in cases of carcinoma of the fundus.

In inoperable cases of carcinoma of the fundus deep x-ray therapy is of value as a palliative agent and for the prolongation of life.

As to carcinoma of the cervix, on the other hand, the preeminent value of radiation appears to be established. At the Cleveland Clinic we now use radiation rather than surgery in the treatment of carcinoma of the cervix, reserving our final judgment until sufficient time has elapsed for a definite comparative study of the end-results.

As the presence of any but a frankly benign tumor of the breast demands the removal of that organ, especially in a patient past middle age, so when an intermittent or continuous uterine discharge occurs in a patient who has passed the menopause, we believe that a complete hysterectomy should be performed at once. Even if the character of the discharge does not appear to indicate the presence of a malignant growth, this operation should be performed without delay.

Our records include 885 cases of carcinoma of the uterus of which 659 have been cases of carcinoma of the cervix.

Ovary: Cancer of the ovary is rarely primary. When it is primary the removal of both ovaries is indicated. If the peritoneum is extensively involved deep x-ray therapy may retard the progress of the disease.

We have confined this discussion to carcinoma of the various organs and tissues. We shall, therefore, not discuss the treatment of malignant diseases of the bones. The relative merits of the treatment of these diseases by radiation or by surgery are still *sub judice* but may finally be decided by means of the data which is being accumulated by the Registry of Bone Sarcoma of the American College of Surgeons.

In conclusion it should be emphasized that whatever his present point of view regarding the method of choice in the treatment of a malignant tumor of any organ or tissue, the surgeon must hold himself in readiness to alter that view if accumulating experience indicates that other methods are to be preferred or are at least worthy of trial. It may be that as the result of the researches — clinical and experimental — which are in progress in many clinics and laboratories, some new and effective measure may be developed of which we should be ready to avail ourselves.

All the vast researches into the cause and cure of cancer have thus far yielded neither an adequate explanation of its primary cause, nor a specific cure. Until that specific cure is discovered, therefore, the one and only method of prevention is the removal of the precancerous condition.

The layman, laying aside morbid fears, must report to his physician any persistent abnormal visible growth or symptoms of abnormal interest; and the internist must instruct his patient that the early and complete removal of the affected parts offers the only hope of cure, and with the surgeon, must carry on in the clinic and laboratory researches for more definite methods of diagnosis and more efficient therapeutic agents. The surgeon, for his part, must develop his technic so that the cancerous growth may be completely removed with the least possible trauma, and must discover further means by which to conserve and increase the vital forces of his patients. As the cancer problem stands today, the disease is to be conquered only by the closest "team play" of these three — the layman, the internist, the surgeon.

JAUNDICE IN HEART DISEASE

A. Carlton Ernstene

Jaundice not infrequently occurs in patients with advanced stages of heart disease. The patients for your consideration today illustrate the diversity of mechanisms responsible for the development of icterus in various cardiac disorders and the importance of the sign in accurate diagnosis, prognosis, and treatment.

In a recent excellent review Rich[1] has divided all cases of jaundice into two groups: retention jaundice and regurgitation jaundice. Jaundice of the retention type develops whenever the liver becomes functionally unable to excrete bilirubin in the amounts presented by the blood for disposal. In this form of icterus, the blood plasma gives the indirect van den Bergh reaction, and the urine does not contain bilirubin or bile salts. On microscopic examination of the liver, the bile ducts are patent, but the liver cells usually show atrophy or cloudy swelling. Jaundice of the regurgitation type results from pathologic changes in the liver which permit the escape of whole bile from bile canaliculi into the blood stream. In this form of icterus, the blood plasma gives the direct van den Bergh reaction, and the urine contains bilirubin and bile salts. On pathologic examination, there is rupture of the bile canaliculi resulting from obstruction of the ducts or from necrosis of the hepatic cells. I shall follow this classification in discussing today's cases.

Jaundice in Nonvalvular Heart Disese with Congestive Myocardial Failure. The bilirubin content of the blood is increased in practically all cases of congestive myocardial failure,[2] and occasionally this increase is sufficient to produce visible icterus. Jaundice, when it occurs, usually is of the retention type and is due to two factors. The first of these is depression of the excretory function of the liver due to the anoxemia resulting from venous congestion. The second is increased production of bilirubin as evidenced by its increased concentration in the blood and its increased excretion as urobilin in the stools and urine.[1]

Case I. The patient before you, a white male, fifty-four years of age, was informed five years ago that his blood pressure was elevated. Dyspnea and palpitation on exertion and edema of the ankles were first noted one year later. Since then he has had several

attacks of congestive failure. Two weeks ago, he developed a cough which was followed shortly by a conspicuous increase in his previous symptoms. For the past week he has had moderate jaundice.

On physical examination there is orthopnea and slight cyanosis. Other significant findings, in addition to the icterus, include fulness of the peripheral veins, signs of congestion at the bases of both lungs, enlargement of the heart with a soft systolic murmur at the apex, and auricular fibrillation. The blood pressure is 200 mm. of mercury, systolic and 120 mm. of mercury, diastolic. The liver is tender, and its edge is felt 6 cm. below the costal margin. There is edema over the legs and sacrum. The urine contains no bilirubin, and the jaundice, therefore, is of the retention type.

The following diagnoses have been made: Essential hypertension, hypertensive heart disease, hypertrophy and dilatation of the heart, congestive myocardial failure, and auricular fibrillation.

It will be noted that in this subject the jaundice is uniform in distribution. This, however, is not always the case, for Meakins[3] observed a number of patients with severe myocardial failure and advanced dependent anasarca in whom jaundice was present only in the upper part of the body while the fluids of edema and ascites rarely contained bilirubin.

The enlargement of the liver in this patient is due, of course, to passive congestion. Gross sections of such livers usually present the so-called "nutmeg" appearance, and microscopic examination reveals atrophy of the central cells of each lobule.[1]

Passive congestion of the liver due to causes other than myocardial failure may also result in the appearance of icterus of the retention type. Extensive pericardial effusion, for example, is accompanied by increased peripheral venous pressure, congestion of the viscera, and occasionally by jaundice.

Jaundice in Congestive Myocardial Failure With Tricuspid Regurgitation. When myocardial failure is accompanied by functional or organic insufficiency of the tricuspid valve, jaundice is almost always present. The retention of bile pigment in this condition owes its origin to precisely the same factors as in nonvalvular heart disease with congestive failure.

Case II. This patient is a schoolboy, seventeen years of age. Evidence of heart disease was first discovered three years ago during a routine physical examination. Six months later he developed symptoms and signs of myocardial failure and was kept in bed for several weeks. He has taken digitalis daily since that time

and has been practically free of symptoms. Three weeks ago he noted increasing dyspnea and palpitation, followed shortly by swelling of the legs and abdomen.

The patient, as you see, has severe orthopnea. The skin and sclerae are deeply jaundiced. The cheeks are flushed, and there is moderate cyanosis of the lips, ears and tips of the fingers. The veins of the neck are distended and pulsating forcibly. There is bulging of the thoracic wall in the precordial region. The heart is greatly enlarged, and systolic and diastolic murmurs are present at the apex and in the right second intercostal space. A loud, harsh systolic murmur is heard in the fourth and fifth interspaces just to the left of the sternum. Auricular fibrillation is present with an apex rate of 120 beats per minute and a moderate radial pulse deficit. The arterial blood pressure is 190 mm. of mercury, systolic and 30 mm. of mercury, diastolic. Capillary pulsation is present, and a "pistol shot" sound is heard over the femoral artery. Signs of pulmonary congestion are present over the back, and there is evidence of free fluid in the right pleural cavity. The liver extends 8 cm. below the costal margin and shows forcible pulsations on bimanual palpation. There is considerable ascites and moderate edema of the legs, thighs, and lower back. The urine contains no bilirubin, and the jaundice, therefore, is of the retention type.

The following diagnoses have been made: Rheumatic heart disease, hypertrophy and dilatation of the heart, congestive myocardial failure, mitral stenosis and regurgitation, aortic regurgitation, tricuspid insufficiency, and auricular fibrillation. The presence of tricuspid insufficiency is indicated principally by the distended, pulsating jugular veins, the expansile pulsations of the liver, and the harsh systolic murmur over the tricuspid area.

Jaundice in Congestive Myocardial Failure With Acute Necrosis of the Liver. In patients with jaundice due to congestive myocardial failure, icterus usually is of the retention type and microscopic examination of the liver reveals only atrophy of the central portions of the lobules. In severe and protracted cardiac failure, however, actual necrosis of the liver cells may be present.[1] Usually only the central cells are thus affected, although occasionally, as in the case to be considered next, the changes are very widespread and the liver presents the pathologic picture of acute necrosis (acute yellow atrophy, acute toxic hepatitis). When the necrosis of the liver cells becomes sufficiently extensive, bile canaliculi are ruptured and permit leakage of bile into the blood stream. The jaundice, therefore, changes from the retention type to the regurgitation type.

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Case III. The case I wish to review is that of a woman, forty-one years of age, who had had rheumatic fever at the age of twelve years. She was admitted to this hospital in January, 1929, with symptoms of moderately severe congestive failure, six weeks in duration. There had been one earlier attack of cardiac failure, five years previously, and since that time she had had dyspnea on exertion. On admission to the hospital there was slight jaundice of the skin and sclerae. This gradually disappeared during her stay in the hospital. The liver was enlarged and could still be felt at the time of discharge, six weeks later. The urine contained no bile. On April 20, 1929, the patient was readmitted to the hospital because of increasing dyspnea, cough, palpitation, and swelling of the ankles, one week in duration. Jaundice and pain in the right upper quadrant of the abdomen had been present for three days, and for two days there had been repeated vomiting. The skin, sclerae, and mucous membranes were deep yellow in color, and there was moderate cyanosis. The heart was enlarged and presented the signs of mitral stenosis and auricular fibrillation. The percussion note was dull, and numerous medium râles were heard over the bases of both lungs. The liver was tender and extended a hand's breadth below the costal margin. There was slight edema over the legs and sacrum. The urine contained a large amount of bilirubin; the blood gave the direct van den Bergh reaction, and the stools were grayish white in color.

The patient was fairly comfortable during the first ten days in the hospital although the jaundice did not diminish. Repeated vomiting then returned, and she rapidly became drowsy and confused. The jaundice increased in intensity, while the liver began to decrease appreciably in size. During the following three days, the patient's condition became progressively worse; the temperature rose to 103 F., and death occurred on the fourteenth day after admission.

Necropsy revealed chronic mitral endocarditis with mitral stenosis, chronic passive congestion of the viscera, early bronchopneumonia, and acute necrosis of the liver. The liver weighed 1560 Gm., was very soft, flabby, and dark purplish red in color. On cut surface, practically none of the normal markings could be distinguished. Microscopic sections showed almost complete disappearance of normal liver cells (Fig. 165). The general appearance was that of a sponge consisting of the original stroma, now filled with blood, with scattered liver cells occurring singly or in small groups in all stages of necrosis. There was no proliferation of the bile ducts and only slight evidence of regeneration of the hepatic cells.
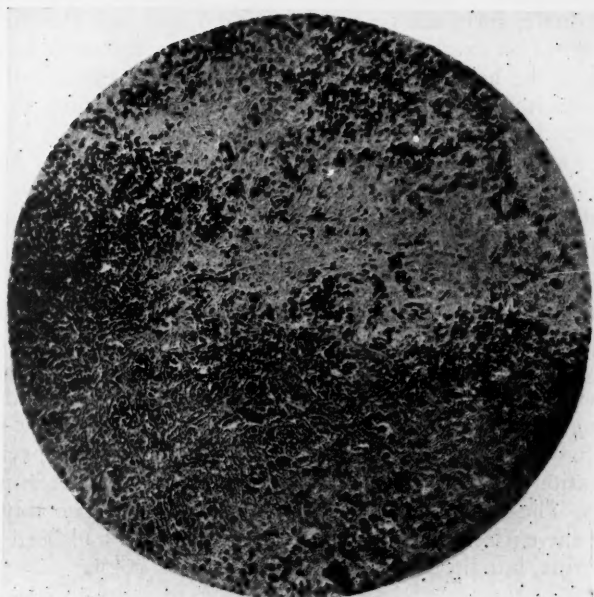
Fig. 165.— Photomicrograph showing widespread necrosis of the hepatic epithelial cells in Case III

In severe and prolonged passive congestion the liver may become abnormally susceptible to the effects of toxic agents. Although no definite statement can be made, it is possible that the terminal bronchopneumonia in this patient contributed to the production of the widespread necrosis of the hepatic epithelial cells.

You will note that at the time of the patient's first admission to the hospital, the jaundice was of the retention type, while during the second admission, it had the characteristics of the regurgitation type and reflected the more extensive liver damage then present.

Jaundice in Congestive Failure With Pulmonary Infarction. The rapid development or intensification of jaundice in congestive failure usually is due to pulmonary infarction. Infarction of the lung causes a sudden increase in the degree of anoxemia of the liver which, of course, reduces the already impaired excretory function of the hepatic cells. In many instances, the increase in anoxemia causes actual necrosis of the liver cells in the center of the lobules; and if this is sufficiently extensive, the jaundice assumes the characteristics of the regurgitation type.[1]

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Case IV. The patient whose necropsy specimens I have here was a white male, forty-six years of age, who had had chronic cough and dyspnea on exertion for ten years. During the week before admission to the hospital, these symptoms had increased and edema of the legs had been present. On physical examination, there was orthopnea, moderate cyanosis, and slight jaundice. The heart was enlarged with systolic and diastolic murmurs at the apex. Auricular fibrillation was present. There were signs of congestion at the bases of both lungs and of consolidation in the left midchest posteriorly. The liver extended almost to the level of the umbilicus, and there was edema of the legs and over the lower back.

During the first two days in the hospital, the jaundice increased greatly. Then for twelve days it gradually diminished as the patient's general condition improved. On the fourteenth day, however, there was an abrupt increase in dyspnea and cyanosis, and on the following day the jaundice was noted to be much more intense. There had been no cough, pain in the chest, or hemoptysis, and examination of the chest revealed no significant changes in physical findings. The patient became comatose and died two days later. During the entire period of observation, bilirubin had been present in the urine, but the stools had been of normal color.

Necropsy confirmed the diagnosis of rheumatic heart disease with mitral stenosis. The liver was enlarged and congested and showed necrosis of the central cells of the lobules in microscopic sections (Fig. 166). The major portion of the cavity of the left auricle was occupied by a large, grayish-red, friable thrombus, and the lumen of the right inferior pulmonary vein was occluded by an attached thrombus which extended peripherally for a considerable distance along its tributaries. The lower lobe of the right lung was completely infarcted; it was deep red in color and of a firm, rubbery consistency throughout. Scattered through the remainder of the lungs were many areas of thrombotic infarction, ranging from a few milliameters to 5 or more centimeters in the greatest diameter. There were no areas of pneumonia.

Both the rapid increase in jaundice soon after the patient's admission to the hospital and the sudden intensification of icterus a few days before death presumably were due to pulmonary infarction. It is to be noted that during the entire period of observation the icterus was of the regurgitation type and indicated the presence of central necrosis of the liver.

Although severe anoxemia of the liver cells is the principal cause of the sudden appearance of intensification of jaundice in
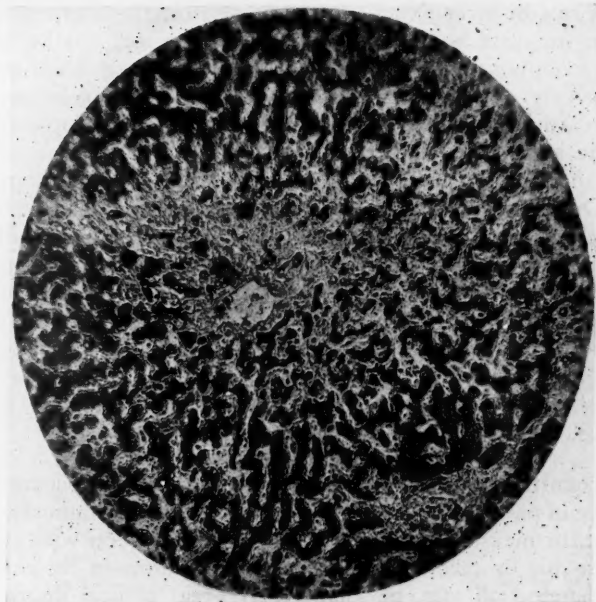
Fig. 166.— Photomicrograph showing necrosis of the central hepatic
epithelial cells in Case IV

myocardial failure with pulmonary infarction, it is to be remem-
bered that hemorrhagic infarcts are sources of bilirubin. The ex-
tensive infarction in the present case must have added appreciably
to the total amount of circulating bilirubin and thus increased the
degree of jaundice.

Jaundice in Subacute Bacterial Endocarditis. Prolonged febrile
illnesses accompanied by the development of severe anemia cause
atrophy of the central hepatic cells and depress the excretory func-
tion of the liver. At the same time, the increased destruction of red
blood cells causes a considerable increase in bilirubin production.
Jaundice of the retention type may result from the combination of
these two factors.[1]

In subacute bacterial endocarditis, the skin often has a diffuse
yellowish-brown color to which the term "café au lait" is applied.
Occasionally, if the disease is accompanied by a sufficiently severe
anemia, the skin and sclerae become definitely icteric. This has oc-
curred in the last patient to be presented.

Case V. Fifteen years ago, at the age of seventeen years, this man had rheumatic fever. Nine months ago he began to tire easily and to have frequent night sweats. He was admitted to the hospital nearly five months ago because these symptoms had increased progressively. The important physical findings included slight pallor, cardiac enlargement with the cardiac and peripheral signs of aortic regurgitation, petechiae in the conjunctivae, a palpable spleen, microscopic hematuria, moderate leukocytosis, and irregular fever. During the time in the hospital his condition has become progressively worse, with great loss of weight, repeated chills, and numerous showers of petechiae. On two occasions he has complained of severe pain in the left upper quadrant of the abdomen. Repeated blood cultures have yielded growths of Staphylococcus aureus. The red blood cell count has decreased to 1.8 millions per cubic millimeter. The skin now has a definite yellow color, and the sclerae show slight icterus. The urine contains no bilirubin, and the jaundice, therefore, is of the retention type.

Recognition of the factors responsible for the occurrence of jaundice in patients with heart disease is of value in indicating what therapeutic measures are to be employed. In subjects with retention jaundice due to uncomplicated myocardial failure of the congestive type, venesection may be followed by great clinical improvement and subsidence of the icterus. The diminution in jaundice under these circumstances is due to decreased passive congestion of the liver and consequent alleviation of the anoxemia of the hepatic epithelial cells. Jaundice probably would occur less frequently in congestive failure if venesection were done routinely in all subjects in whom the venous pressure is higher than 20 cm. of water and the red blood cell count is within the limits of normal. Icterus due to pulmonary infarction complicating congestive failure indicates the presence of severe anoxemia. The administration of oxygen frequently is of considerable benefit in this condition. Jaundice occurring with extensive pericardial effusion indicates the necessity for aspiration of the pericardial fluid. Removal of the fluid results in a decrease in venous pressure and therefore relieves the anoxemia of the liver. In addition to these measures, all patients with congestive heart failure should, of course, be treated by rest in bed, complete digitalization, limitation of fluid intake and, if necessary, administration of diuretic drugs. Icterus in patients with subacute bacterial endocarditis may diminish following transfusion and other therapeutic measures directed toward alleviation of the anemia.

The cases that have been presented illustrate the multiplicity of mechanisms that may result in the appearance of jaundice in

patients with heart disease. I believe it will be apparent to you that the recognition of the form of jaundice in each instance is of considerable importance not only in estimating the type and degree of pathologic change in the liver but also in determining the diagnosis, the prognosis, and the proper treatment.

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THE INTERRELATION OF ALLERGY AND OTOLARYNGOLOGY

W. V. Mullin

Allergy, defined by Pirquet[1] as altered reactivity of cells and tissues, is perhaps the most popular term used to define a large group of unpleasant symptoms affecting about 10 per cent of our population. The word atopy, meaning "strange disease," used by Coca and Cooke[2] to describe these symptoms, is very appropriate, for a strange disease it surely is. The term "vasomotor rhinitis" hardly describes the disease, and if cases thus designated are carefully and properly studied, some specific cause for the symptoms can usually be discovered. Although much that has been said about allergy is purely theoretical, many facts, based on practical observations and experience, are known. I shall not offer any discussion of the theories regarding this disease, but shall confine myself to a consideration of these known facts, especially as they pertain to the joint field of the internist and the otolaryngologist. Too often skin tests alone are relied on for a diagnosis and as an index to treatment, without sufficient consideration of the role of the sinuses in the production of the symptoms and of their relation to the treatment.

For this reason, although allergy may affect the cells of any part of the body and produce symptoms referable thereto, the symptoms of chief concern in this paper are those that involve the nose, the sinuses and the tracheobronchial tree.

There is a marked tendency for the disease to occur in a child whose mother and father are both allergic; in such a case the symptoms are more marked, and the treatment is accordingly more difficult. The choice of the right treatment and its success will depend on proper diagnosis, and there is no short route to diagnosis. A definite plan of examination must be followed in every case. A detailed and carefully elicited history is absolutely essential. This should include the family history, a description of the patient's environment and the time at which the first symptoms were noticed. If these symptoms are more marked at night or early in the morning, something in the patient's room or home should be suspected as the cause. If they are worse during the day, something in the patient's occupation may be the causative factor. If symptoms are first noticed during the summer months, the pollens should be sus-

pected. The patient should be asked whether relief has ever been secured by changing his environment. The history alone may determine what protein substance should be suspected.

Next to the history and symptoms, the appearance of the nasal mucosa is important. It will be found to be peculiarly pale and edematous, and when once this sign is fixed in the mind's eye of the examiner, its appearance will always make him suspicious of the presence of allergy. It must also be kept in mind that the appearance of the mucosa over the turbinals and the septum is an indication of the condition of the membrane that lines the sinuses, and therefore the sinuses should be examined carefully. The condition of the sinus mucosa may be due to allergy, and a secondary purulent infection may exist on the surface and in the cavity of the sinus. This is particularly true of cases of long standing. An x-ray picture of the sinus may be misleading if it has been taken during an attack of allergy, and it may not indicate accurately the true thickness of the mucosa, as Proetz[3] has so well demonstrated. By means of the injection of iodized poppy seed oil 40 per cent, Proetz showed a case in which the antral membrane, which had previously been normal in thickness, became thickened a few hours after the patient had suffered an attack of asthma, almost obliterating the sinus cavity.

On the roentgenogram, the allergic membrane may look as if a cyst or polyp were present. I have records of cases in which edema of the nasal mucosa was seen; the membrane fell into folds and gave the characteristic appearance of early polyp formation. On roentgen examination, the maxillary sinuses were found to be opaque and appeared as if granulations were present. I have seen the entire membrane return to its normal appearance and the sinuses become clear as the result of the elimination of the foreign protein, which in one case proved to be derived from feathers.

The next step in the examination should be the skin test, which should be made by one who is especially trained in this work. The proper interpretation of reactions is essential. By referring to the carefully recorded history of the patient, the necessity for a large number of tests may be greatly reduced. Entire reliance should not be placed on the skin reactions, for, as has been indicated, they constitute only one part of the examination. Scratch tests should be made first, and if the reactions are negative, intradermal tests should be made. If positive reactions are obtained that coincide with the history and environment of the patient, and if the symptoms of allergy disappear, when he is not allowed to come in contact with the offending proteins, what could be more satisfactory?

But one must be prepared for the following conditions: The skin may be allergic and other parts of the body may escape sensitization, or the reverse may be true; the nasal and bronchial mucosa may be sensitive while the skin is not. In some cases the skin may be hypersensitive and may show multiple reactions even to substances to which the patient is never exposed. This is particularly true in regard to pollens.

The skin tests may be positive when the patient is symptom-free. The patient who presents a typical history and symptoms of allergy and whose reaction to skin tests is negative presents a difficult problem. If on examination of the nasal secretions eosinophils are found in abundance, and if the blood shows eosinophils amounting to more than 4 per cent, the probability that allergy is present is increased. The examination of the stained blood smear for eosinophils must be made by one who is well trained in this procedure.

In the cases studied by my associates and myself we have confirmed the ether reaction of the urine described by Barber and Oriel,[4] which consists of the finding of a proteose substance in the urine during the acute or paroxysmal stage of allergic conditions. However, I do not find that this test can be relied on sufficiently for it to have any diagnostic value.

In the course of the examination, time should be taken to explain to the patient what allergy really is, what a difficult problem it presents, that improvement is not easily attained, and that therefore he must become interested in his own problem, study his own environment and cooperate in every way with the physician. If no positive reactions are found and no infection is found in the sinuses, it may be necessary to resort to eliminative diets.

Every allergist should have a sufficient knowledge of botany to be able to advise his patient how, when and where he can avoid the wind-borne pollens to which he is sensitive, for he must either do this or be made immune to them by treatment. That bacteria and their products cause sensitization and allergic reactions is questioned by some. I believe that they do, for I have seen cases in which I have felt sure that the teeth and sinuses were responsible. In this connection, the following case is presented.

Report of a Case

A middle-aged woman had nasal obstruction due to a typical allergic condition of the nasal mucosa. A feeling of tightness in the chest was gradually developing, and a few asthmatic symptoms were present. All skin tests, both scratch and intradermal, gave negative results. The eosinophil count amounted to 6 per cent, and the nasal

secretion showed many eosinophils. A roentgen examination of the sinuses showed the left maxillary sinus to be completely opaque, and the presence of a large cyst or polyp was suspected. Cultures from the nasal secretion were made, and a group of nondescript organisms was found. The patient was tested with an antigen made from these organisms, and the reaction was negative. The left antrum was washed, and only a small amount of secretion was obtained, from which a culture was made and Streptococcus was grown. The patient was tested with this antigen, and no reaction was obtained. A culture was likewise made from the stool, and a negative reaction was obtained. The left maxillary sinus was operated on by making an opening through the canine fossa, and a large cyst was exposed, the contents of which were aspirated and implanted on Rosenow's brain broth; the cultures, however, were sterile. A portion of the cyst wall was then implanted on the brain broth, and a streptococcus was grown. When the patient was tested with an antigen made from this streptococcus, the reaction of the skin was positive.

COMMENT

This case bears out a statement that I have made that from an absorptive standpoint the infection within the lining membrane of the sinus is more important than the free pus within the cavities of the sinus.

All cases of bronchial asthma are not due to allergy. A review of 315 cases of bronchial asthma studied at the Cleveland Clinic showed that allergy was present in 164; in 97 definite, proved infection was present in the nasal accessory sinuses, and in 54 there was neither allergy nor infection in the sinuses. In this unclassified group, some nervous reflex was believed to be present which imparted undue stimulation to the vagus nerve and the sympathetic nervous system, thus accounting for the asthmatic paroxysms.

It is conceivable that if the nasal and sinus mucosa is allergic for a long period of time, it will become infected and degenerate. The decision as to when an operation should be performed on an allergic sinus always calls for good judgment. If the cause for the allergy is found and eliminated, does the membrane have the power to restore its function? If it has this power, operation should not be performed. In early cases of allergy, operation should not be resorted to until every possible effort has been made to find the cause of the allergy and to remove it. In patients who cannot be relieved from their symptoms as long as their sinuses are filled with infected membrane, operation should be performed. If it is felt that the sensitivity is due to bacteria, operation should be performed.

In some cases of our series, vaccines seemed to be of benefit, cultures being taken from the infected sinus. In bronchial asthma, a culture is also taken from the tracheobronchial tree. Whether these vaccines act in a specific manner or as a foreign protein is a question that I am unable to answer. At the Cleveland Clinic all of the cases have been studied as to the possibility of an endocrine dysfunction, and no basis for glandular extract therapy has been found. The same statement holds true in regard to calcium.

In conclusion, it may be stated that allergy presents an increasingly perplexing problem which required combined study by the otolaryngologist and the internist and the utmost cooperation on the part of the patient.

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FOCAL INFECTION AS A FACTOR IN HEART DISEASE*

RUSSELL L. HADEN

All possible etiologic factors in cardiac failure warrant thorough consideration since heart disease is today by far the most frequent cause of death. Clark[1] states that in the year 1928 the number of deaths from heart disease in certain states having an aggregate population of 25,000,000 was 228 per 100,000 persons as compared with 106 from kidney disease, 105 from cancer and 100 from pneumonia. He adds that the number of deaths from heart disease in the registration area of the United States doubled during the eight year period from 1917 to 1925, while the population increased by only one-third.

Many deaths from heart disease are due primarily to valvular disease resulting for the most part from activity of the virus of rheumatic fever. In other cases, death results from vascular syphilis or is the end result of arterial hypertension. A very large proportion of the deaths from heart disease result, however, from chronic changes in the myocardium which we group under the term chronic myocarditis, or chronic myocardial degeneration, often ascribed to senescent changes. Impairment of the blood supply secondary to coronary artery disease is an important factor in the development of the myocardial changes. Often, however, the cause is not apparent. I wish to emphasize one possible factor, namely, chronic focal infection, which is often overlooked or its importance underestimated.

Rheumatic infections of the heart valves and heart muscle are focal in origin in the sense that they usually metastasize from infection in the nasopharynx. These infections occur typically at an early age although their effects may be apparent only late in life. The proper care of tonsil and dental infection has seemingly definitely decreased the incidence of rheumatic fever and consesequently of rheumatic heart disease. It is not, however, the virus of rheumatism which I wish to discuss and emphasize but other infections of focal origin, largely streptococcic in type.

All students of heart disease are aware of the effect of infection

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on the heart muscle. It may be accepted as axiomatic that in every acute infection a certain degree of myocardial degeneration takes place. Recovery from this change may be complete but often the acute disturbance in the heart muscle is followed by fibrosis or scar tissue formation in the myocardium. It is probably for this reason that chronic fibrous myocarditis is the heart lesion most commonly observed. The acute myocarditis seen so often in diphtheria and the characteristic carditis of rheumatic fever and chorea are known to everyone. Other types of infection might be mentioned in which manifest acute involvement of the myocardium is frequently seen. These types are easily recognized. The slow chronic poisoning from a focus of infection is less spectacular and not so easily recognized but is equally disastrous in its end results.

Under the head of focal infection I do not include the infections of rheumatic fever as these are not due to a chronic focal infection in the commonly accepted use of the term although they usually arise in nasopharyngeal lymphoid tissue. Rheumatic infections occur usually before the age of 30. It is after this period that chronic septic foci are much more common and most disastrous. Few of us escape them. Dental infection increases at this period, tonsil infection may continue, and infections in the gall bladder, the sinuses, the cervix, the prostate, and the appendix may develop. From such areas, absorption of bacteria and their toxins may go on for a long period, often for years, with constant damage to the heart.

A chronic focal infection is practically always due to the non-hemolytic streptococcus. Such an infection does not cause the primary valvular disease which is typical of the rheumatic virus, but may give rise to bacterial infections of valves already damaged by the rheumatic virus. Typically and most frequently, however, focal infections cause chronic myocardial disease, which is characterized by degeneration of muscle fibers and replacement by fibrous tissue. The action is essentially the same as that occurring in the case of various acute infections. The action is slower and more prolonged but the final result is much the same. In chronic joint disease we appreciate the effect of long continued absorption from a chronic focus of infection but often forget that the myocardium may be similarly affected over a long period of time resulting in a chronic fibrosis. The marked effect of such infection is often brought to light by the added element of some other acute infection such as influenza, which removes the final margin of safety.

Further proof concerning the relation of septic foci to heart disease may be adduced experimentally by:

(1) The results of injection of animals with bacteria from septic foci; (2) attempts in selected cases to reproduce in animals

the heart lesion from which the patient suffers by the injection of bacteria recovered from foci in the patient; and (3) therapeutic results obtained by the removal of foci from patients suffering from heart disease presumably of focal origin.

In studying some problems in dental focal infection I injected 1500 rabbits intravenously with bacteria from periapical infection. The organisms were principally nonhemolytic streptococci. Each

Fig. 1.— (A) Culture from periapical dental infection in glucose-brain agar. Note the uniform growth of colonies throughout the tube; (B) Culture similarly made in which the organism present will grow only under partial oxygen tension as shown by the absence of growth at the top of the tube; (C) Photomicrograph of characteristic nonhemolytic diplococcus from dental infection.

animal received 5 c.c. of a 24-hour broth culture and was autopsied in from three to six days. The organisms were grown under partial oxygen tension (Fig. 1), a point most important in preserving pathogenicity during the period intervening between removal of the bacteria from the body and the injection of it into the experimental animal. All gross lesions observed at the routine autopsy

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TABLE I

Localization of bacteria Isolated From Dental Infection

Number of Animals	Number of Patients	Percentage of Animals Showing Lesions In:							
		Joint	Kidney	Muscle	Endo-cardium	Myo-cardium	Brain	Eye	Stomach and Duodenum
1500	501	58	30	21	18	10	4	14	16

were tabulated (Table 1). In this series, 18 per cent showed gross endocardial lesions and 10 per cent showed lesions in the myo-
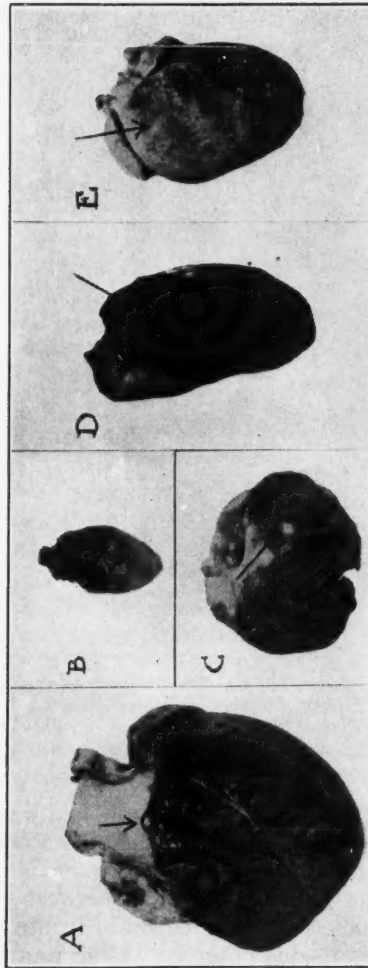
Fig. 2.— Heart lesions in the rabbit produced by the intravenous injection of bacteria from periapical dental infection. (A) vegetations on aortic valve; (B) pericarditis; (C) large vegetation on mitral valve; (D) multiple hemorrhages in right auricle; (E) massive necrosis of wall of right ventricle.

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cardium. The lesions recorded are only those which are visible to the naked eye (Fig. 2). If microscopic studies had been made the incidence of lesions in the myocardium would certainly have been much higher. The myocardial lesions observed were hemorrhage, sometimes limited to the right auricle, areas of necrosis of the heart
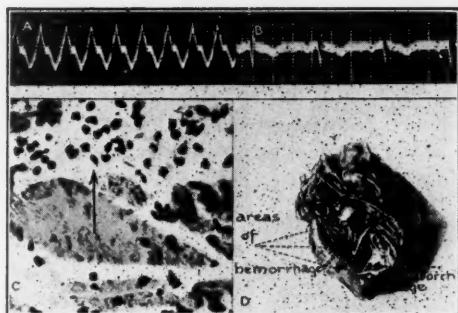
Fig. 3.— (A) Electrocardiogram of patient (Case 1) taken during an attack of paroxysmal tachycardia; (B) electrocardiogram of same patient taken one month after the attack; (C) photomicrograph of patient's heart muscle obtained at autopsy. Note the area of polymorphonuclear infiltration; (D) heart of rabbit injected with streptococcus from an abscess around a partially erupted third molar tooth of the patient.

muscle, and occasionally small abscesses. It seems apparent from such results that the organisms in chronic septic foci are well able to produce disease of the myocardium and heart valves.

The results of animal inoculation with organisms recovered from chronic foci in patients suffering from heart disease of probable focal origin are best illustrated by case reports. The following are typical examples:

CASE I

Acute Myocarditis

A medical student, twenty-four years of age, stated that he had had several acute attacks of rapid heart beginning at the age of twelve years. There was no history of coincident infection at the onset. At the age of eighteen an attack occurred while the patient had an abscessed tooth. In May, 1925, he had an attack lasting several hours during which electrocardiograms were taken. These showed the tachycardia to be of a ventricular type (Fig. 3, A). For several weeks before this attack he had had an infection around a partially erupted third molar tooth. A second electrocardiogram

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taken in June, 1925, showed a normal heart rate but evidence of myocardial disease (Fig. 3, B).

At this time the third molar tooth was removed, revealing a pocket of pus from which a pure culture of a streptococcus was obtained. Two rabbits were injected with this culture. One died forty-eight hours later. At autopsy numerous areas of hemorrhage were found in the heart muscle (Fig. 3, D). The other animal was killed and at autopsy a smaller number of hemorrhages were found in the heart muscle.

In October, 1925, the patient died during another attack. At autopsy the heart showed no gross lesions. Sections, however, showed areas of acute infection in the heart muscle (Fig. 3, C).

CASE 2

Acute Auricular Fibrillation

A banker, sixty-five years of age, had been having attacks of acute auricular fibrillation for only a short period of time. He had otherwise been in excellent health. The general physical examination was negative except for the heart condition. He had had some indefinite gastric symptoms. There was no hypertension. The dental radiographs showed three pulpless teeth only one of which showed radiographic evidence of infection. All three teeth were extracted. Only two, the upper right and left second biscuspids (Fig. 4, A) were cultured. Both showed a profuse growth of streptococci.

Two animals were injected with 5 c.c. each of the broth culture of the streptococcus recovered from the upper right second bicuspid. One animal was killed five days later. The examination showed a large vegetation on the tricuspid valve (Fig. 4, B) and hemorrhages in the myocardium. There were also hemorrhages in the first part of the duodenum, a few cortical kidney abscesses, purulent fluid in the large joints, and some areas of necrosis in the muscle. The second rabbit was killed six days after injection. There were vegetations on the tricuspid valve and in the right auricle (Fig. 4, C). The joints showed very slight involvement. There was one small abscess in the medulla of one kidney and some necrosis in the muscle.

Two rabbits were also injected with the diplococcus recovered from the upper left second bicuspid. In one, hemorrhages were seen in the papillary muscle of the left ventricle (Fig. 4, D), vegetations and hemorrhages in the endocardium of the right auricle, and some infection around the joints. The other animal showed vegeta-

tions on the heart valves and some small focal lesions in the myocardium. A few lesions were also found in the kidney medulla and there was involvement of the joints and muscles.
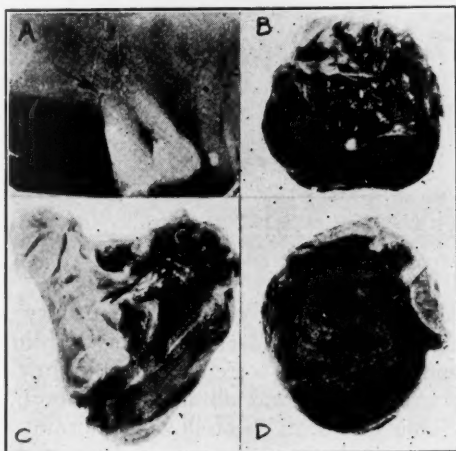
Fig. 4.— (A) X-ray negative of pulpless tooth of patient (Case 2) which showed a profuse growth of streptococci on culture; (B) vegetations on tricuspid valve of rabbit injected with culture; (C) heart of another rabbit similarly injected showing multiple vegetations and hemorrhages in the wall of the auricle; (D) hemorrhage in myocardium.

CASE 3
Acute Myocarditis and Phlebitis

A physician, sixty years of age, had had a phlebitis of the left femoral vein in 1904 following an acute alveolar abscess. Following this there were frequent flare-ups of the dental infection without further signs of systemic disease. In 1914 he began to have anginal attacks which continued up to 1916. These attacks were entirely relieved by the removal of an infected tooth. In March, 1923, the root of the bicuspid tooth became infected, and following this the patient had a recurrence of the phlebitis and anginal attacks. In June, 1923, nonhemolytic streptococcus was recovered from the blood. The patient became progressively worse, myocardial insufficiency developed, and death ensued. At autopsy multiple infarcts were found in the heart muscle.

After the extraction of the bicuspid root, the infection of which had initiated the present illness, cultures were made from the socket and two rabbits were injected. The culture showed only a green-
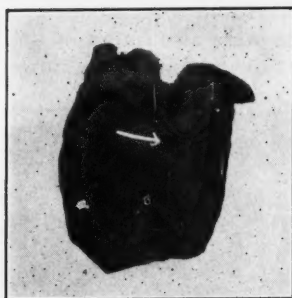
Fig. 5.— Vegetation on heart valves of rabbit injected with cultures in Case 3. This heart also showed necrosis of heart muscle.

producing streptococcus. The rabbits at autopsy showed only endocardial vegetations and infarcts of the myocardium. The upper right second and third molars were extracted in July, 1923. A profuse growth of streptococci was obtained from both. Two rabbits were injected. One was dead the following morning. The autopsy revealed only multiple hemorrhages at the base of the valves. The second rabbit was dead forty-eight hours after injection. The examination showed only vegetations of the heart valve (Fig. 5).

The tendency of bacteria recovered from active dental infection in patients suffering from heart disease of focal origin, to cause valvular and myocardial lesions in the experimental animal is striking and adds evidence of a causal relation of the septic foci to the systemic lesion. The results in a group of patients with heart and vascular disease so studied are shown in Table 2.

TABLE 2

Localization of Bacteria From Dental Infection in Heart and Vascular Disease

Group	Number of Animals	Number of Patients	Percentage of Animals Showing Lesions In:							
			Joint	Kidney	Muscle	Endocardium	Myocardium	Brain	Eye	Stomach and Duodenum
I*	1210	405	60	32	22	17	9	5	14	14
II†	40	10	60	25	22	63	50	2	8	14

*Group I. Animals inoculated with dental cultures from patients not known to be suffering from heart or vascular disease.
†Group II. Animals inoculated with cultures from teeth of patients suffering from heart or vascular disease.

Little evidence concerning the causal relation of a chronic focus to the heart affection is obtained from the results of removal of septic foci. In acute cases there may be a striking therapeutic

result. All too often no evident good results are obtained from the removal of the focus because the heart lesion has developed over a long period of time with permanent damage which may not be undone. Here the most to be hoped for is the prevention of the extension of the injury.

The important lesson to be learned from a study such as this is the realization on the part of the clinician of the potential danger to the heart of chronic septic foci. If this is kept in mind the importance of removal of focal infection early instead of late is apparent. There seems to be no doubt that the judicious removal of septic foci will do much to lessen the incidence of heart disease especially of the myocardium. In patients in whom the heart valves are already damaged by the rheumatic virus the removal of foci of infection should lessen also the incidence of subacute bacterial endocarditis. Early removal of chronic foci cannot be stressed too strongly in all diseases of focal origin. Too often the late removal is disappointing and the importance of chronic foci is underestimated because the systemic disease, although of focal origin, is beyond repair. Systemic disease of focal origin should be cured before it develops.

SUMMARY

Chronic infection in teeth, tonsils, gall bladder, genito-urinary tract, and sinuses is an important factor in the causation of disturbances of the myocardium and in secondary infections of the heart valves.

Organisms recovered from chronic foci of infection caused heart lesions in a large percentage of rabbits injected intravenously.

Bacteria obtained from chronic foci in patients with heart disease due to focal infection produced heart lesions in a very high proportion of rabbits injected intravenously.

The therapeutic results of late removal of chronic foci are disappointing because the lesion caused by the focus is so often permanent.

The early removal of chronic foci should lessen the incidence of heart disease.

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THE TREATMENT OF CARCINOMA OF THE CERVIX

Thomas E. Jones

On scanning the literature since 1900 on the treatment of cancer of the cervix one finds that three periods are represented. During the first period the surgical treatment was emphasized and the reports consisted chiefly of descriptions of operations and surgical end-results. Then there was the period of controversy concerning the relative merits of surgery and radium. During the past ten years, in this country, and with few exceptions on the continent, most of the literature has dealt with radiation therapy, its technic and end-results. An analysis of these results would seem to indicate that, for the time being at least, radium and roentgen ray is the treatment of choice, not only from the standpoint of the rate of curability but also from the standpoint of palliation, morbidity and economy.

In this paper, I am reporting a series of 420 cases of cancer of the cervix, in which the patients were examined, treated and observed during the period from 1920 to 1931, inclusive. In this group, there were 302 cases of primary carcinoma, in eighty there were recurrences following operation or irradiation elsewhere and in eighteen, the lesions were too far advanced for any possible treatment. Twenty patients in this group refused treatment or sought medical advice elsewhere.

I shall not take time to discuss the diagnosis of carcinoma of the cervix. It has been dwelt upon time after time. Yet, on reviewing my series of cases, it is not pleasant to have to admit that in patients examined in 1931 the disease was just as far advanced as it was in those examined in 1920. This in spite of numerous articles written on the subject and in spite of the publicity given it by The Society for the Control of Cancer. Despite the fact that the cervix is an easily accessible organ, failure to recognize early cervical cancer has occurred in a discouraging number of cases. Delinquency on the part of the patient is sometimes responsible, but with increasing public education this is becoming less frequent and still entirely too many failures are attributable to the remissions of the medical profession.

Diagnostic failures come about in two ways. The symptoms may be attributed to the menopause and frequently consultation with-

out proper examination leaves the patient with a false sense of security which leads to further delay. The lesion may be discovered but may not be recognized as malignant, being mistaken for ulcer, erosion or eversion. In case of doubt a biopsy is imperative. The physician's hesitancy to do a biopsy may have resulted from the active discussion a few years ago of the danger of spreading the cancer in this way. Today that discussion is dead — so are many patients for lack of a biopsy. I have never seen any harm come from it and recommend its use in any doubtful case. It will save far more than it will harm.

Another fallacious opinion has been advanced in an effort to show that irradiation both by roentgen-ray and radium may cause distant metastases not seen heretofore. The literature shows that many distant and bizarre metastases were observed long before radium was used. If metastases are being observed more frequently now, it is because radiation has prolonged the life of the patient for sufficient time to make this observation possible. On noting the cause of death in my series it is found that practically all the patients have died with the disease confined to the pelvis with obstruction to the ureter only. Very few show metastases to the liver, lungs and bones.

Anyone who has treated a large group of cases is at once impressed by the varied individual resistance to cancer. Some patients with apparently advanced lesions respond better than do those in whom the disease is recognized early. This variation in response is undoubtedly attributable to normal body defenses about which little is known. However, Broders has developed a method of evaluation of malignancy histologically, by which the prognosis in a given case may be expressed on a numerical basis, dividing the cases into four groups, according to the degree of cellular differentiation. Following these lines, a tremendous amount of investigation has been carried on by other workers for the purpose of determining whether there is any definite relationship between the histologic structure of carcinoma and its relative malignancy, and of trying to deduce from this finding the best form of treatment for the type in question, and also of determining the prognosis. I have not been able to test this out in my series of cases because I believe that a large personal equation enters into the problem and that direct, personal contact with Broders would be necessary in order to develop a precise duplication of his method. If not done properly, I am sure that such an attempted classification would lead to further confusion. Another complication, of course, is that sections from different portions of the tumor may give different histologic pictures which also may be misleading.

The clinical classification I use is that of the American College of Surgeons which, for working purposes, is quite practical except in regard to the question of involvement of the broad ligaments. It is often difficult at first examination to decide whether or not such involvement may be inflammatory or malignant, but time generally furnishes this information. I believe that cures in cases in which there is definite infiltration of the broad ligament are relatively few.

Rationale and Technic of Radium Therapy

For practical purposes, the simple idea that radium is a means of destroying cancer cells without too much injury to the normal cells is a good working hypothesis, but by reason of our accumulating knowledge of the physics of radiation, and of the biologic effects of radiation, we are being led to a better understanding of its action. In brief, radium has a threefold action on malignant tissue. It affects (1) the cancer cells, (2) the connective tissue, and (3) the blood and lymph vessels. The action on the cancer cell is shown microscopically by swelling and vacuolization of the protoplasm and by shrinking of the nuclei. This is followed by phagocytosis and absorption and replacement by an homogeneous connective tissue. This contracts and affects the lymphatic and smaller blood vessels and starves the growth.

There is not sufficient time to enumerate the varieties of technic which have been used since radium therapy was instituted nor to mention all the men who have contributed to the advancement of our present knowledge. Suffice it to say that there are two entirely different schools of thought in regard to the method of treatment. In one, the opinion is that it is best to give large, massive doses within a short space of time, preferably in one, or at most, two treatments. The other is that it is preferable to give very small doses over a longer period of time. I believe that most of the large clinics in this country favor the former view, while protagonists of the latter method are led by Regaud of the Radium Institute of Paris. This difference of opinion undoubtedly will be settled before many years elapse, when the results of both methods may be compared. Standardization of the dosage of radium used in treating uterine cancer is impractical; dosage and technic must vary with the character and location of the lesion.

The technic followed in the Cleveland Clinic has varied but little during the last ten years, the only change being that since a larger amount of radium has been available, larger doses have been given over a shorter period of time, and an effort is made to give the complete dose at one sitting. Previously, the total irradiation was given

in two doses. The average dose given in the first cases in my series was 4200 milligram hours distributed evenly in and against the cervix. In later cases, since radium has been combined with roentgen ray of high voltage the average dose is about 3,600 milligram hours. The standard screen is made of brass, one and one-half millimeters in thickness, and this is encased in a rubber tube three millimeters thick. At the present time a tube is placed in the fundus as well as in the cervix. This is done because in some cases treated earlier it was found that after being free from symptoms for a year or so, the patient suddenly might have bleeding and discharge, and examination would reveal a large undermined cavity at the upper end of the vagina which had not been reached by the radium. It is necessary to anesthetize the patient in order to determine accurately the extent of the new growth. However, it is sometimes impossible, even when the patient is under an anesthetic, to place a tube of radium high in the cervical canal.

In addition to the radium tubes placed in the fundus and cervix, two or three tubes are placed against the cervix and these are held in place by packing the vagina tightly with gauze. If the growth is of the cauliflower type it is frequently curretted away or implanted with radium needles. A catheter is placed in the bladder in order to keep it empty and as far away from the radium as possible. Care should be taken in transferring the patient from the table to the cart and from the cart to the bed. Bending and twisting of the patient during the transfer may dislocate the vaginal tube and may account for bladder and rectal symptoms. The best method is to place the cart alongside the table and to slide the patient on the cart by means of a sheet, and to transfer her from the cart to the bed in the same manner, so that the position is unchanged throughout the procedure. Gold seeds have not been used in the treatment of any of these cases, but they are of great value in cases in which there has been recurrence, because their action is localized to a greater or lesser extent. Large, heavily filtered doses frequently are harmful in the treatment of lesions which have recurred. In this series there has been no case in which gold seeds were placed in the broad ligaments by laparotomy. Three to four weeks after treatment with radium the patient returns to the Clinic for a course of treatments with high voltage roentgen rays, given in five or six doses during a period of five or six days.

After patients have been treated they are requested to return at monthly intervals for three months, and afterwards, every three months during the following year. If local recurrences develop, they are treated by means of implantation of seeds. If the recurrence is deep, roentgen therapy is repeated, with marked relief for a time.

In cases of intractable pain in the pelvis and down the legs, cordotomy may be done. Section of the sensory column in the cord may afford amazing relief from pain.

COMPLICATIONS

The chief complications in the treatment of carcinoma of the cervix by radium are hemorrhage, symptoms referable to the rectum and bladder, and fistulae, both urinary and fecal.

Hemorrhage may be due to the natural progress of the disease or to ulceration caused by the radium. I believe that the natural progress of the cancer is the principal cause of hemorrhage. In the most serious cases packing and transfusion are sufficient to control the hemorrhage.

Bladder and rectal symptoms are of two types — early and late — and it is quite important that they should be recognized. It is reasonable to assume that if a sufficient dose of radium is given to cure carcinoma of the cervix, it will also be sufficient to produce an erythema in the rectum or bladder. Very often this erythema is slight and passes unnoticed unless the patient is questioned. If it is severe, it is evidenced by a slight burning sensation and a tendency to frequency of urination or defecation. In the mild cases, the condition usually clears up within ten days or two weeks, but in the severe cases from four to six weeks may be required. It is in this group in which the symptoms persist that late rectal and bladder complications may develop, usually six or eight months after the initial irradiation. These late symptoms frequently are mistaken for a recurrence of the carcinoma, and if the patient is given additional treatment with radium, irreparable damage may result. A clue to the true state of affairs is found in the fact that the symptoms are out of all proportion to the findings. There is severe pain and tenesmus and the stool contains considerable blood and mucus. Digital examination causes greater pain than in the case in which there is recurrence of the malignant lesion. The patient is not cachectic. Proctoscopic examination reveals, approximately at the level of the cervix, a puckered scar or small ulcer with telangiectasis and considerable redness of the mucosa. The condition may be compared to an overtreated area on the skin which is healed by the formation of scar tissue through which fine vessels may be seen to course. In the rectum the scarring is subject to trauma and infection with subsequent ulceration which causes the late symptoms.

The same general condition is to be found in cases in which there are late bladder symptoms. Cystoscopic examination may reveal an area of intense redness and, at times, ulceration. I have observed several cases of this type over a period of months, and a

few over a period of two years. Occasionally the urinary salts will be found deposited in the slough in the bladder and stones will be formed. For the rectal symptoms the treatment consists of rest in bed, cleansing of the lower bowel, and the injection of three or four ounces of warm olive oil into the rectum twice a day. Occasionally an opium suppository is necessary. For the bladder symptoms rest, irrigation of the bladder, and the instillation of gomenol are prescribed. Sometimes these bladder and rectal complications may not disappear for four to six months.

Fistula. We know that the natural progression of carcinoma of the cervix will cause a certain number of fistulae into the rectum or the bladder. In some of my earlier cases fistulae may have resulted from treatment of the carcinoma, but with our present knowledge and the improved methods of treatment, I feel sure that the incidence of fistula will be lower than in cases in which the patient has received no treatment at all. If the fistula appears soon after treatment it is interpreted as being due to destruction from the disease. If it appears late, and there is no evidence of recurrence of the carcinoma, it probably is due either to progressive ulceration or to the later complications mentioned above, and hence is the direct result of the radium treatment.

The method of treatment of a fistula in the rectum must depend upon its size and the amount of inconvenience it causes the patient. A small fistula may not require treatment. If a large fistula is present, it may be advisable to do a colostomy before attempting to repair it, and to close the colostomy if and when the repair is successful.

The urinary fistula is more annoying on account of the constant flow of urine. If the fistula is small, it can be repaired easily by operation. If it is irreparable, the patient may be made more comfortable by transplantation of the ureters into the sigmoid.

Of the total number of cases of primary carcinoma of the cervix coming to the clinic some attempt at treatment has been made in 93 per cent. The remaining 7 per cent were in extremis on admission. Below in tabular form are the statistics of the results in 303 cases of primary carcinoma of the cervix treated from 1920 to 1931, inclusive. All patients not traced are counted as dead. It will be seen that of 148 cases treated over five years ago, 37 or 25 per cent are alive and well. Twenty-nine per cent are living from three to five years, and 61 per cent are living under three years.

With increasing facilities throughout the country to take care of these patients, it seems to me that our biggest problem still remains, that of getting the patients to seek medical advice when the disease is still in an early stage.

RESULTS IN TREATMENT OF CARCINOMA OF THE CERVIX

	Year	Treated	Traced	No. Living	Per Cent
Living over 5 years.....	1920	8	8	2	25
	1921	17	15	4	24
	1922	22	21	5	23
	1923	26	23	5	20
	1924	24	21	7	30
	1925	21	17	5	25
	1926	30	25	9	27
		148	130 - 90%	37	25%
Living 3 to 5 years.....	1927	32	26	9	28
	1928	13	10	4	30
		45	36 - 80%	13	29%
Living 1 to 3 years.....	1929	48	42	24	50
	1930	35	31	19	54
	1931	32	32	28	87
		115	105 - 90%	71	61%

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HYPERTHYROIDISM SHOWING CARBOHYDRATE METABOLISM DISTURBANCES

TEN YEARS' STUDY AND FOLLOW UP OF CASES

HENRY J. JOHN

For several decades writers in this country and abroad have reported the coincident finding of glycosuria in some cases of hyperthyroidism. Joslin and Lahey,[1] in their recent study of 500 cases of disease of the thyroid, reported the occurrence of glycosuria in 38.6 per cent of 228 cases of primary hyperthyroidism and in 27.7 per cent of 83 cases of adenomatous goiter with secondary hyperthyroidism, as compared with only 14.8 per cent in 189 cases of nontoxic goiter and 13.6 per cent of patients without diabetes or any disease of the thyroid gland. In a series of 100 dextrose tolerance tests which I[2] did in 82 cases of hyperthyroidism and 10 cases of colloid goiter, there was a fasting glycosuria in 19 per cent. In table 1 are given the reports of various authors as to the incidence of glycosuria in cases of hyperthyroidism.

TABLE I

Glycosuria in Hyperthyroidism

Author	Number of Cases	Percentage of Cases Showing Glycosuria
Marsh	....	2.0
Joslin and Lahey:		
Primary hyperthyroidism	228	38.6
Secondary hyperthyroidism	83	27.7
Nontoxic goiter	189	14.8
Schulze	16	25.0
John: present publication	100	19.0
Bryan:		
Toxic adenoma	244	3.2
Nontoxic adenoma	982	1.0
Exophthalmic goiter	361	1.1

When chemical analyses of the blood began to be generally used, hyperglycemia, either with or without glycosuria, was demonstrated in sporadic cases of hyperthyroidism. A review of the literature showing the incidence of hyperglycemia in hyperthyroidism (table 2) shows a great discrepancy in the findings of different investigators.

TABLE 2
Incidence of Hyperglycemia in Hyperthyroidism

Author	Number of Cases	Percentage of Cases Showing Hyperglycemia
Fitz	1,800*	0.5
Wilder	2,340*	0.6
Von Noorden and Isaac	1,000	0.6
Wilder	1,131†	2.0
Sattler	....	3.0
Lund and Richardson	29	3.4
John: present publication	9,000	6.88
John: 1928	3,335	8.5
Mojarova	84	25.3
Flesch	....	60.7
Geyelin	27	90.0
Total	18,746	

*Exophthalmic goiter.
†Toxic adenoma.

Experimental studies on animals made to determine the relation of the thyroid gland to the blood sugar content showed that extirpation of the thyroid gland leads to a lower blood sugar level, while, on the other hand, the injection of thyroxin, the feeding of hashed thyroid gland to animals or the injection of thyroid extract produces hyperglycemia. In other words, various workers tried to duplicate the clinical finding of hyperglycemia in the syndrome of hyperthyroidism. Many observations regarding the thyroid-blood-sugar relation in human beings are recorded.

The incidence of hyperthyroidism among cases of diabetes is comparatively low, as can be gleaned from table 3, the average being 1.68 per cent. A diabetic patient is, of course, subject to the same ailments as is a nondiabetic person. The incidence of diabetes among cases of hyperthyroidism, on the other hand, is a fairly consistent figure, as can be gleaned from table 4, and is nearly twice as high as the general incidence of diabetes.

The present study comprises clinical and laboratory observations made over a period of ten years, including an intensive study made during the period from January 1, 1925, to October 1, 1931. During this time, about 9,000 cases of thyroid disease have been seen in the Cleveland Clinic, most of which were cases of hyperthyroidism (exophthalmic goiter, adenoma with hyperthyroidism). Of this group, 620 cases, or 6.88 per cent, showed some degree of nonphysiologic hyperglycemia (fasting or two and one-half hours or more postprandial) either with or without glycosuria. During

TABLE 3
Incidence of Hyperthyroidism in Diabetes

Author	Number of Cases of Diabetes	Number of Cases with Hyperthyroidism	Percentage
Greeley	614	6	0.97
Joslin and Lahey	4,917	..	....
Primary hyperthyroidism	....	43	0.87
Toxic adenoma	....	28	0.57
Simple goiter	....	4	0.08
Wilder	1,249	..	....
Primary hyperthyroidism	....	14	1.10
Toxic adenoma	....	22	1.80
Rabinowitch	3,000	24	0.80
Von Noorden	1,000	30	3.00
Murphy-Moxon	827	8	0.96
Average			1.68

TABLE 4
Incidence of Diabetes in Hyperthyroidism

Author	Thyroid Disease	Diabetes	Percentage
Joslin and Lahey: total hyperthyroidism	5,908	75	1.26
Primary hyperthyroidism	1,751	43	2.5
Secondary hyperthyroidism	....	28	4.3
Sattler	1,866.	56	3.0
O'Day	....	4	....
Fitz	1,800	9	0.5
John: all thyroid diseases	9,000	207	2.3
Average			2.31

these years, it has been the practice of my associates and myself to make a routine blood sugar estimation in every new case, as this gave much information about many unsuspected cases of diabetes which would not have been picked up otherwise. Most of the cases, which showed some degree of nonphysiologic hyperglycemia, were then followed up and studied further for a period up to ten years. These data I am offering here.

When the 620 cases showing nonphysiologic hyperglycemia were followed up further, it was found that in some cases the hyperglycemia was present in only the primary examination and that in some others the hyperglycemia disappeared without any medication. Consequently, these cases are not included in my consideration. In some other cases the patients have not been observed for a long enough period to be included in this series. In some cases inadequate data were available, and for that reason they are not

included. Intensive observations over a period of from one to ten years were made on 166 cases which alone are included in this special study. All of these showed a definite disturbance of carbohydrate metabolism. The number of years the patients in this series have been under observation is shown in table 5.

TABLE 5

Length of Observation on 166 Cases of Hyperthyroidism and Diabetes Over a Period of Years (John)

Years of observation....	1	2	3	4	5	6	7	8	9	10
Number of cases.......	82	32	19	11	8	4	1	—	1	8

By a very conservative estimate, however, I should say that about 200 cases showed what might be called definite hyperglycemia like that of diabetes. In some of these cases the hyperglycemia was purely functional in type and therefore disappeared in a few weeks or months after thyroidectomy on dietary treatment alone or combined with insulin, but — as further experience taught me — the hyperglycemia would not have disappeared in all cases without such treatment. In the total of 620 cases of hyperthyroidism in which hyperglycemia was present, it remained in 30 per cent and disappeared in 70 per cent. This makes the incidence of diabetes in this series of cases of thyroid disease 2.1 per cent, a figure that is close to the average incidence of diabetes in cases of hyperthyroidism as reported in the literature (2.3 per cent). Thus, of this series approximately 200 patients remained diabetic and had to be treated as such, and 35.7 per cent of them are still taking insulin in order to control the diabetic state.

This summarizes briefly the problem and is an answer to those who try to offer an academic discussion of this subject, which, interesting as it may be from the standpoint of the laboratory, cannot be fully adopted by a clinician who has to treat these patients, many of them for the rest of their lives.

This point is well illustrated by the report of Sattler,[3] who in 1909 collected 56 reported cases in which diabetes was associated with hyperthyroidism. Thirty-seven of these cases had been followed for a sufficient length of time to afford positive information. Of these 37 cases, in 24 (64.8 per cent) there was a fatal termination within comparatively short periods of time, and in 7 cases the patients died in coma.

The incidence of diabetes in this special series of 166 cases and its distribution, according to sex and decades, are given in table 6. The highest incidence is in females, as one would expect, since the highest incidence of hyperthyroidism occurs in females. As for the age distribution of the associated occurrence of diabetes and hyper-

TABLE 6

Incidence of Diabetes and Hyperthyroidism and Its Distribution
According to Sex and Decades (166 Cases; John)

Age decade	II	III	IV	V	VI	VII	Percent-age
Male	..	1	9	11	8	5	20
Female	1	4	13	37	53	23	80
Total	1	5	22	48	61	28	
Percentage	0.6	3.0	13.2	28.9	36.7	16.8	....

Joslin and Lahey: Male, 19 and female 81 per cent.

thyroidism, I have tried to discover how it compares with the age incidence of diabetes without hyperthyroidism, and I have found that the two curves run quite parallel, as shown in chart 1. This suggests that hyperthyroidism does not play any important etiologic role so far as the age incidence is concerned. Table 7 shows clearly the priority in appearance of hyperthyroidism, which occurred in 85.5 per cent in primary hyperthyroidism and in 51.9
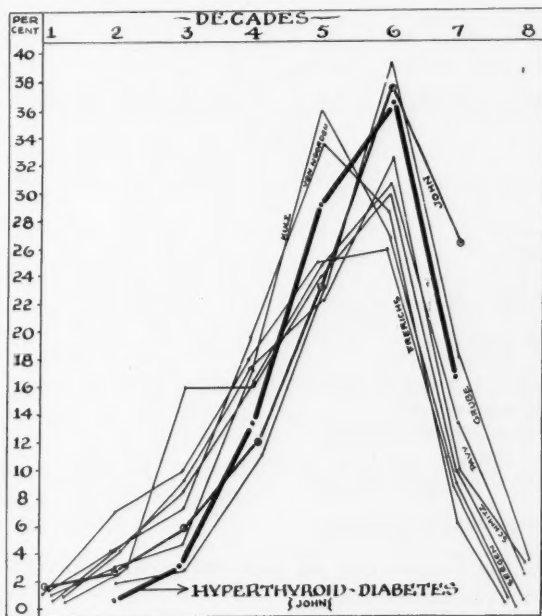

Chart 1.— The incidence of diabetes in various decades according to eight authors.

TABLE 7

Priority in Appearance of Hyperthyroidism or Diabetes in 152 Patients, According to Joslin

Condition	Number of Cases	Hyperthyroidism Precedes Diabetes	
		Number of Cases	Per-centage
Primary hyperthyroidism:			
Fitz, primary and secondary not differentiated.................	22	21	95.5
Wilder.........................	12	9	75.0
Joslin-Lahey....................	28	23	82.1
Total......................	62	53	85.5
Secondary hyperthyroidism: Toxic adenoma			
Wilder.........................	19	9	47.4
Joslin-Lahey....................	8	5	62.5
Total......................	27	14	51.9
Sattler.........................	56	37	66.0

TABLE 8

Analysis of 166 Cases of Hyperthyroidism and Diabetes (John)

	Percentage
Male..	20.0
Female..	80.0
Diabetes severe in...	31.0
Diabetes mild in..	69.0
Hyperthyroidism severe in..................................	35.0
Hyperthyroidism mild in...................................	65.0
After thyroidectomy:	
Diabetes improved in.................................	55.0
Of these still taking insulin........................	23.5
Diabetes more severe in..............................	30.0
Of these still taking insulin........................	46.0
Diabetes stationary in................................	15.0
Of these still taking insulin........................	62.0
All patients still taking insulin...........................	35.7

per cent in toxic adenomas, an observation that may have an important etiologic significance.

In table 8 I offer an analysis of the 166 cases in this series in order to show the progress of the patients. After thyroidectomy 55 per cent of the patients improved as far as their diabetic status

was concerned; in 15 per cent the diabetic condition remained stationary, and in 30 per cent the patients either required more insulin or, if not taking insulin, it is but a question of time until insulin will have to be administered. As stated, 35.7 per cent of the entire group are still taking insulin.

It is obvious that glycosuria in itself does not tell a great deal regarding the status of the carbohydrate metabolism unless one knows also the blood sugar response to the ingestion of carbohydrates and the level of the renal permeability to sugar. In a series of 100 dextrose tolerance tests which I did some years ago[2] in 82 cases of hyperthyroidism and 10 cases of colloid goiter, 66 per cent of the curves indicated an impaired tolerance. In a larger series of 239 cases of hyperthyroidism which I published in 1930,[4] 63.5 per cent showed an impaired tolerance. Such an incidence is high and ranks as high as obesity (65.6 per cent). The renal threshold, on the other hand, estimated in 180 cases of hyperthyroidism, was low; thresholds for sugar below 180 occurred in 81.1 per cent of the cases. The average renal threshold was 147. The excretion of sugar by a patient with a low renal threshold is usually of little or no significance. The measure of sugar excretion by the application of Allen's paradoxical law,* however, does throw some definite light on the differentiation of glycosuria in this group of cases and is of distinct value, as Rabinowitch has shown. However, I should offer a caution as to any hurried diagnosis until such a case has been followed up over a sufficiently long period for one to make sure of his premises, as no single laboratory functional test should ever be considered as final.

Hepatic Lesions Associated With Hyperthyroidism

The liver in a case of hyperthyroidism is supposed to be glycogen-poor; it either does not bind dextrose or else lets it go too readily, or there is such an enormous demand for the dextrose in the body that it is rapidly used up and has no chance of being stored in the liver. In an editorial in the *Annals of Internal Medicine,*[5] regarding the hepatic lesions associated with exophthalmic goiter, the author brings out the following points: "Patients dying in exophthalmic goiter show some degree of simple or pigmented atrophy, but the most marked change was the very frequent occurrence of marked diffused fatty degenerative infiltration bearing all the earmarks of a severe toxic process (like the classic phosphorus liver). The heart and the kidneys presented a marked fatty degenerative infiltration." The author explained these changes as being

*The more the carbohydrate taken by a diabetic patient, the less is utilized.

the result of acute disturbances in the oxygenation of the body resulting from or dependent on the syndrome of exophthalmic goiter. "The livers further show at times a peculiar form of chronic parenchymatous hepatitis in the form of lymphocyte infiltration, bile duct proliferation and increase in stroma of the islands of Glisson." To study these changes, Weller[6] studied 44 autopsies on patients who had shown no condition other than hyperthyroidism; his report is shown in table 9, which was presented before the Association of American Physicians in 1930.

TABLE 9
Weller's Data

	Hyper-thyroidism	Controls
Number of cases showing no hepatitis.................	6	30
Number of cases showing slight or moderate hepatitis.	16	13
Number of cases showing well marked hepatitis......	22	1

Weller summarized his findings as follows:

A well marked chronic parenchymatous hepatitis was found at autopsy in 22 of 44 selected cases of Graves' disease, while but one case of the same degree of hepatic lesions was found in a control series of the same number of autopsies. In the Graves' disease group, only six showed no evidence of hepatitis while in the control series 30 out of the total of 44 cases showed no hepatitis. The coincidence of hepatitis with exophthalmic goiter is therefore significant and is in accord with clinical observations of the occurrence of functional disturbance of the liver in cases of Graves' disease.

Simonds and Brandes[7] rendered dogs thyrotoxic by heavy thyroid feeding (for from thirty-two to one hundred days). The livers of these dogs were practically devoid of glycogen.

Asher[8] found that in animals made absolutely free from carbohydrate by thyroid feeding and phlorhizin, the addition of fat to the food increased the output of sugar. From this he decided that the hyperthyrotic liver possesses the ability to form glycogen but cannot fix it so that after its formation it gives it up.

Charvàt and Gjurič,[9] who studied the problem of carbohydrate metabolism in hyperthyroidism, came to the conclusion that the liver in cases of exophthalmic goiter is the cause of hyperglycemia because it does not bind its glycogen in a stable manner, its glycogen is labile and the tissues burn dextrose well; furthermore, in order to use up as much of the circulating dextrose as possible, the renal threshold in hyperthyroidism is raised.

These authors offered as an explanation that in exophthalmic goiter a condition of liver shock is present in which the glycogen-

poor liver binds glycogen very loosely and lets go of it easily, whereas the tissues in patients with hyperthyroidism need sugar badly as a ready and excellent supply of energy; moreover, sugar does not burden the organism with any specific dynamic action as do fats and proteins. As the liver through the lability of its dextrose causes a marked hyperglycemia, the renal threshold is easily crossed and theoretically glycosuria should result in all cases. This, however, is not the case, as Charvàt and Gjurič have shown, for the threshold rises in order to enable the tissues to use up a greater portion of the dextrose.

In view of their experiments the authors studied the arterial and the venous blood sugar for a period of several hours after the injection of physiologic solution of sodium chloride in normal persons and in patients with diabetes and again in cases of hyperthyroidism. In normal persons they found that without the injection of saline the arterial and the venous sugar fluctuates but inappreciably. After the injection of saline into normal persons, the discrepancy between arterial and venous blood is also slight (chart 2). They said that such an injection is not sufficient to mobilize the sugar, either in the tissues or in the liver.

On the other hand, the injection of saline into patients with hyperthyroidism presents a more interesting picture (chart 2). Here there is a definite dissociation between the arterial and the venous sugar. The arterial sugar rises higher than the venous sugar, which rises but little or may even be decreased. Such an injection causes shock to the liver, to which it answers by releasing its labile glycogen into the circulation. That this is in reality the liver sugar and not the tissue sugar is shown by the fact that the arterial blood sugar rises, whereas the venous sugar is not changed. There is thus a certain surplus in the arterial blood which is caught by the tissues and does not reach the venous blood. It is a well-known fact that dextrose itself is the best stimulant for the utilization of dextrose by the tissues. Charvàt's former work[10] showed that the burning of dextrose in the tissues of patients with hyperthyroidism is very active.

In the case of diabetic patients the picture is somewhat change.d In such a case the arterial sugar does not rise as markedly as is the case in hyperthyroidism and the curve often approaches that of normal persons. The venous sugar, on the other hand, is higher than the arterial sugar (chart 2). According to Gjurič's view, in cases of severe diabetes the tissue rather than the liver binds the sugar in a labile manner and releases it easily into the venous blood, which consequently is higher than the arterial sugar. In this manner
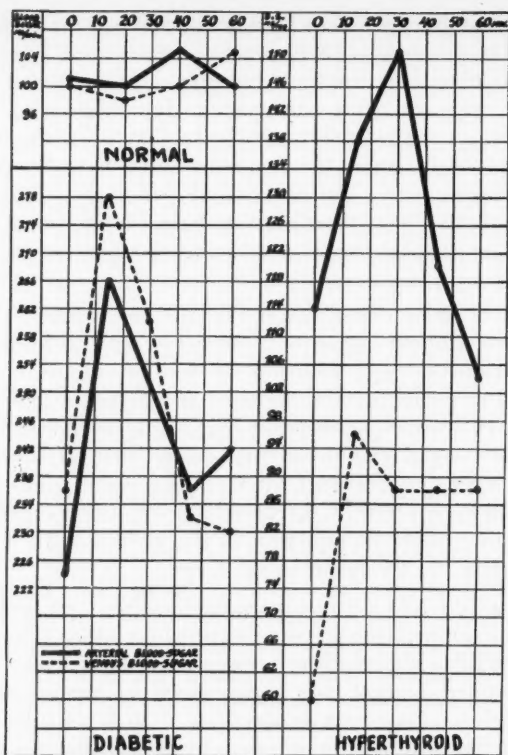
Chart 2.— Curves after the injection of 1 cc. of physiologic solution of sodium chloride per kilogram of body weight. (After Charvát and Gjurič.)

the glycoregulatory disturbance of the patient with hyperthyroidism differs markedly from that in diabetes.

That the liver is not the chief factor in the production of hyperglycemia in hyperthyroidism is suggested by the following points:

1. The incidence of hyperglycemia in hyperthyroidism is too low.

2. The incidence of hyperglycemia in hyperthyroidism is irregular; severe cases usually show no hyperglycemia; mild cases may show pronounced hyperglycemia. If the liver were the primary factor, the degree of hyperglycemia would be proportionate to the severity of the hyperthyroidism.

3. In general, the renal threshold in patients with hyperthyroidism is low,[4] but the excretion of sugar bears no relation to the

severity of the hyperthyroidism. If the storage function of the liver were at fault, glycosuria would automatically disappear after thyroidectomy, but this does not happen. In 35.3 per cent of the 166 cases reported here, the patients have to continue to take insulin, for even though the condition of the liver has improved, the pancreas still does not function sufficiently.

Ketone Bodies. Thyrotoxic persons who are given a carbohydrate-free diet for two days show a marked increase of ketone bodies in the blood. In the normal person the fasting value of ketone bodies never exceeds 3.5 mg. per hundred cubic centimeters of aceto-acetic acid and 5.5 mg. per hundred cubic centimeters of beta-oxybutyric acid. In the thyrotoxic patient the ketone bodies rise as high as 16 mg. per hundred cubic centimeters of aceto-acetic acid and 18 mg. per hundred cubic centimeters of beta-oxybutyric acid. The patient with hyperthyroidism has a lowered glycogen reserve available for metabolism.

Levulose. Strauss[11] first introduced the determination of alimentary levulosuria as a method for testing the liver function. Isaac and Adler[12] showed experimentally that of all the organs and cells of warm-blooded animals only the liver is capable of transforming levulose into dextrose. According to Isaac, the alimentary levulosuria is dependent on the fact that the part of the levulose which is not converted into glycogen or is not burned, in case of functional inability of the liver to convert levulose into dextrose, passes as levulose into the blood and is excreted as urine.

Kugelmann[13] offered the following conclusion: "We can now say with certainty that the thyrotoxic liver not only suffers severe injury in its glycogen depots but has also lost the capacity to change large amounts of levulose into dextrose and to utilize them later." (See chart 3, which represents Kugelmann's experiments along this line.)

Insulin. Ten units of insulin given intravenously to man causes a rise of blood sugar of from 15 to 20 mg. per hundred cubic centimeters of blood in the first ten minutes, after which it falls. Bürger[14] demonstrated that this primary rise of blood sugar is dependent on the glycogen function of the liver. In none of the cases of exophthalmic goiter studied by the Bürger method by Kugelmann was his initial hyperglycemia seen. This is a further proof of poverty in glycogen in the hyperthyrotic liver.

Rathery, Kourilsky and Laurent[15] have shown that the blood sugar in depancreatized, starved, and starved and phlorhizinized dogs is distributed in the same proportions during the maximum
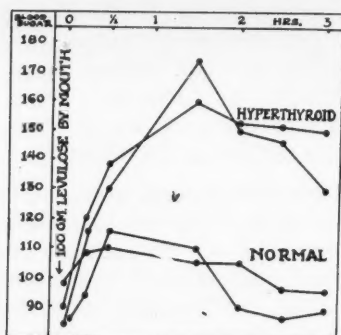
Chart 3.— Blood sugar curves of the administration of 100 Gm. of levulose. (After Kugelmann.)

effect of insulin as in normal animals. The discharge of glycogen from the liver is not influenced by its glycogen content. In dogs under similar experimental conditions, the hyperglycemia immediately following the administration of insulin upsets irregularly the relationship between the blood sugar in different vascular areas.

It would seem that with a little help from insulin the liver gradually resumes its capacity to bind more dextrose and keep a more even blood sugar level. Were it the state of hyperthyroidism alone which brings about the functional change that manifests itself in hyperglycemia, then one would expect the degree of hyperglycemia to bear a direct relation to the severity of the hyperthyroidism, and the incidence of hyperglycemia in cases of hyperthyroidism would be greater than it is. This is not so, however, for some of the most severe derangements of carbohydrate metabolism are found in some of the mildest cases of hyperthyroidism, and many of the most severe and even toxic states of hyperthyroidism show no disturbance of carbohydrate metabolism. Insulin brings about improvement in all cases by its direct action, by its protein-sparing action, through its influence on the storage of glycogen or on the diminution of the ketone bodies, or as the result of all four of these. The fact that disturbed carbohydrate metabolism rights itself in only the mild cases suggests that the protein-sparing function may play a role in the carbohydrate metabolism.

As for the clinical effect of insulin on hyperthyroidism, one may reason that it perhaps improves the patient's general metabolic condition, giving him a better chance to store glycogen in the liver and thus to combat acidosis; to store glycogen in the heart muscle and thus to give it a better chance to do its work; to spare protein by the increased oxidation of dextrose, and to store glycogen in the

muscles and thus eliminate the instability of the organism in general. There is perhaps nothing specific about the action of insulin.

It is a good preoperative measure to give a patient 250 cc. of 10 per cent dextrose made up in saline solution intravenously, together with from 10 to 20 units of insulin, depending on the patient's condition. When the dextrose is buffered with insulin, hyperglycemia does not result even in diabetic cases, as I have shown in my observations on the intravenous administration of dextrose in cases of diabetes and in cases of acidosis as well as in ordinary surgical cases.[16] Such a procedure, therefore, is both logical and helpful, both before and after operation, for the first three days following the operation is the critical period for the patient and a little prevention goes far.

Postoperative Acidosis. Acidosis is a well recognized complication of the postoperative course after thyroidectomy. The pulse rate in such cases is high, and the patient can become semicomatose or stuporous immediately after operation. Is the acidosis in these cases of the same type as diabetic acidosis? Diabetic acidosis is due to the inability of the organism to burn dextrose, this in turn producing an incomplete combustion of fats with the resultant accumulation of ketone bodies in the blood stream (acetone, diacetic acid, beta-oxybutyric acid) and consequent acidosis. In uncomplicated hyperthyroidism, however, there is no such inability to burn dextrose, but there are rather an inability to store glycogen and a general increase of the metabolic process, so that all the available carbohydrate, including the glycogen reserve of the liver and muscles, is often utilized with resultant hypoglycemia. Holman[17] cited a case of hyperthyroidism in which the basal metabolic rate was plus 29 and plus 35 per cent, on two occasions. After thyroidectomy the pulse rate rose to between 180 and 250 immediately after operation, this very high rate lasting for sixty hours. Twenty-four hours after the operation the patient was in a semicomatose condition, and her blood sugar at that time was found to be only 48 mg. per hundred cubic centimeters. Dextrose solution, 20 per cent, was administered, and immediately the patient became conscious. Six hours later the patient again went into a deep stupor. She was again given dextrose, and again immediately became conscious. It is clear that in this case the stupor was due to hypoglycemia, a condition similar to the hypoglycemia of an insulin reaction. This is a condition that should be borne in mind. Blood sugar studies during the post-operative period are often of great value as they tell the needs of the patient at that time.

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Basal Metabolism. The relationship of the basal metabolic rate to the dextrose tolerance in a series of cases of thyroid disease is shown in table 10. It will be noted that in 60.6 per cent of the cases

TABLE 10

Relation of Basal Metabolic Rate to Dextrose Tolerance Tests in 66 Cases of Thyroid Disease (John)

	Normal Basal Metabolic Rate	Increased Basal Rate, Percentage									Total	Per-centage
		10	20	30	40	50	60	70	80	90		
Number of cases....	3	11	8	11	10	10	4	4	4	1	66	....
Diabetic...........	2	5	3	7	5	8	3	4	2	1	40	60.6
Normal............	1	6	5	4	5	2	1	0	2	0	26	39.4

analyzed the dextrose tolerance curve was diabetic or prediabetic in type, while the basal metabolic rates ranged from minus 3 to plus 90 per cent. The case in which the metabolism was minus 3, however, was one of simple goiter and not one of hyperthyroidism. In 39.4 per cent of the cases the dextrose tolerance curve was normal in type, and the basal metabolic rate in these cases varied from minus 3 to plus 80 per cent. On the basis of this study it seems evident that the height of the basal rate bears no relation to the carbohydrate metabolism. The mild derangements of the carbohydrate tolerance that have been observed in this series of cases may be but functional disburbances. They may disappear only in part when hyperthyroidism is eliminated either by operation or by other treatment, thus showing that there is something other than the hyperthyroidism that is playing a part.

COMMENT

I think that the explanation of the disturbed carbohydrate metabolism associated with hyperthyroidism is not found in the state of hyperthyroidism per se, but that it is due rather to some other factor which I believe is a "diabetic anlage" that was present in the patient before the hyperthyroidism developed; infection or obesity would have brought about the same disturbance. Thus Naunyn,[18] in 1917, made the following statement: "I consider it justifiable to draw the conclusion that the thyroid causes glycosuria only where there exists a predisposition (anlage) to diabetes."

The following statement has been made by von Noorden:[19] "Pure hyperthyroidism in the presence of a fully normal chromaffin system and a normal pancreas will very seldom produce an alimentary and spontaneous transitory glycosuria."

It is possible that in hyperthyroidism, in which one is dealing with such an unstable nervous system, the nervous regulatory mechanism may also enter into the picture. But even so, the same problem is presented. Why is it that hyperglycemia occurs in some of the mildest cases of hyperthyroidism and is not present in many of the most severe cases?

Again one may raise the question whether in hyperthyroidism one may be dealing also with hypersuprarenalism, a condition that is known to produce hyperglycemia. In some of the mild cases in which the hyperglycemia disappears after thyroidectomy, the hyperglycemia might well be due to this cause. However, were the hyperglycemia due primarily to hypersuprarenalism, one would find a much higher incidence of hyperglycemia than is found and this again would be relative to the severity of hyperthyroidism, which is not the case.

The question that is unsettled today is whether any of the factors mentioned could induce diabetes when there is no "diabetic anlage" to start with. I think not, but it is not known at present, as the background on which to base a proper interpretation of the facts that confront one and with which one has to deal is lacking.

The incidence of diabetes in hyperthyroidism is 2.1 per cent. The incidence of diabetes at large is given as 1 per cent. There is thus a 100 per cent increase of diabetes in cases of hyperthyroidism. I am inclined to think that a big factor here is the question of over-eating, which is automatically brought about by the increased metabolism demanding more calories, and as the patient starts losing weight he automatically tries to compensate for this by eating more. This throws a great load on the insulogenic apparatus, which, if normal and with a good reserve, stands it well; if the reserve is small, it easily becomes exhausted and diabetes results. The condition is similar to obesity (over-eating), in which, too, the incidence of diabetes is high, and the two are analogous pictures, their end-result being the same, though in one the patient is thin and in the other fat. Also the incidence of diabetes in hyperthyroidism is high from the fifth decade on, when one has to consider the problem of arteriosclerosis and endarteritis, which no doubt are contributory factors to functional changes in the insulogenic apparatus.

The medical problem involved in mild cases of disturbed carbohydrate metabolism is to protect persons with a decreased carbohydrate tolerance, rather than to let them drift along, unprotected toward diabetes. They should be under surveillance until the physician has satisfied himself that stability has been established.

In most of these cases the glycosuria disappears after thyroidectomy. and the carbohydrate tolerance is restored to normal; in others, this does not happen. It is important, therefore, to make postoperative examinations in order to determine whether or not the carbohydrate metabolism has been restored to normal, and when this has not happened to institute such measures as are indicated. It is much easier to keep a diabetic patient in the mild stage of diabetes on a mild dietary routine (for that is all that is necessary in most mild cases) than to treat him successfully after a severe stage of diabetes has developed.

Summary

1. No dextrose tolerance curve is specific for hyperthyroidism. That is, a definite diabetic type of curve may be present in a mild case of hyperthyroidism and a normal curve may be present in a very severe case of hyperthyroidism.

2. A single blood sugar estimation, when such a patient is first seen, is no criterion for the evaluation of or even for a diagnosis of diabetes in such a patient. This serves merely as a lead which should be followed up further and the true state of the patient determined. Even a high blood sugar may be just an incidental finding that clears up quickly, and another much lower blood sugar may persist as a definite diabetic condition.

3. The diagnosis of diabetes in cases of hyperthyroidism can be made only when such a patient has been studied over a sufficiently long time to determine a persistence of the defective carbohydrate metabolism. Without such a time element, many faulty diagnoses of diabetes are bound to occur.

4. Thyroidectomy lowers the total metabolism and in consequence improves the carbohydrate tolerance. In cases in which little or no improvement follows thyroidectomy this is due to the fact that lack of proper diabetic treatment or insufficient treatment has followed the operation, or else that intercurrent infections have produced further damage to the pancreas.

5. If diabetes develops after thyroidectomy, it is due either to other extraneous factors such as produce diabetes in other cases or to the fact that an insufficient amount of thyroid tissue has been removed and an active stage of hyperthyroidism persists. In the latter case, when more of the gland is removed, the diabetes is improved.

6. Hyperthyroidism plays a fundamental etiologic role in the disturbances of endocrine equilibrium in cases with a diabetic

anlage in which diabetes can be precipitated. The factor here may be the heavy ingestion of food which accompanies active hyperthyroidism, thus placing a heavy load on the insulogenic function.

7. Glycosuria and hyperglycemia (either fasting or more often two and one-half hours after a meal) are not uncommonly present in hyperthyroidism. When found they should not be disregarded, but their significance and their relationship to the carbohydrate metabolism should be determined by appropriate tests.

8. The presence of hyperglycemia two and one-half or more hours after a meal, if it persists, is usually an expression of an insufficient insulogenic function.

9. The intervention of the menopause in a case of hyperthyroidism may cause hypertrophy of the islands of Langerhans with the resultant cure of a coincident diabetes. This probably, however, is a rare occurrence, for but few cases are reported in the literature (Rohdenburg[20]).

10. The glycogen depletion of the liver in hyperthyroidism increases the tendency to acidosis and makes a mild case of diabetes temporarily appear as a severe case. This factor is aggravated in cases in which diabetes is present. The ingestion or the intravenous administration of dextrose before or after operation, with or without insulin, according to the indication in the individual case, would seem to be a logical procedure. The factors that influence the glycogen depletion are probably the following:

(a) Toxic influences which directly affect the parenchyma of the liver cells.

(b) A high metabolic rate which causes increased consumption of carbohydrate and depletes the insulogenic stores, with resultant depletion of the glycogen store in the liver. Such a depletion is also shown in uncomplicated cases of hyperthyroidism which do not show a high blood sugar.

11. Hypersuprarenalism may also play a part in the production of hyperglycemia.

12. Patients with hyperthyroidism in whom a frank diabetic condition of severe type is not present, but merely a mild degree of disturbance of the carbohydrate metabolism, may have but "functional" diabetes or again they may have early diabetes. If appropriate treatment is not given, a frank diabetic state may develop.

13. The administration of thyroid preparations is not without danger. It may precipitate hyperthyroidism, and may even produce diabetes.

14. In my series of 100 dextrose tolerance tests in 82 cases of hyperthyroidism and 10 cases of colloid goiter, fasting glycosuria was present in 19 cases and absent in 81 cases. Sixty-six per cent of the curves indicate an impaired tolerance.

15. From the observations of these patients it would appear that the renal permeability is decreased in the active stage of hyperthyroidism. The renal threshold for dextrose was below 120 mg. per hundred cubic centimeters of blood in 35.6 per cent of the patients studied. The average renal threshold in cases of hyperthyroidism was 147 mg. per hundred cubic centimeters of blood.

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CARBOHYDRATE IN THE TREATMENT OF POSTOPERA-
TIVE TETANY, WITH SPECIAL REFERENCE
TO LACTOSE

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McCullagh, Ph.D.

The usual methods of treatment of postoperative tetany are
not entirely satisfactory. To any who have experienced the dif-
ficulties in the management of this condition, the need of simpler
effective measures is apparent. The oral administration of calcium,
even in large doses, is not always sufficient to control the symptoms,
and repeated injections of it over long periods is undesirable or
impossible. Injections of parathyroid extract alone or in addition
to calcium may be effectual, but are inconvenient and expensive.
Methods are reported here for the control of phosphate metabolism
to an extent that will afford distinct benefit to patients suffering
from this disease.

Serum Calcium

The best-known and perhaps the most satisfactory single
criterion by which the severity of parathyroid tetany may be
judged is the degree of depression of the level of total serum calcium.
Examination of a large series of serum calcium levels in tetany
makes the fact apparent, however, that the symptoms do not
necessarily parallel the total calcium levels. This confirms the
opinion of John.[1]

It is known that the total serum calcium can be raised and
frequently brought to normal in tetany by the feeding of large doses
of calcium. In some of our cases the symptoms were not controlled
by these measures, and their severity was thought to be out of pro-
portion to the calcium level. This was especially striking since a
patient might be symptom-free with a certain calcium level on one
day, while on another occasion, although the serum calcium was
at the same height, symptoms might be present. Abnormally high
levels of blood phosphates accompanied nearly normal calcium
values in some of these cases.

Blood Inorganic Phosphates

Ver Ecke[2] in 1898 noted a lessened phosphate excretion in the
urine in tetany. This has received ample confirmation by Sal-
vasen,[3] Greenwald,[4] and others, and it is now recognized that one

of the constant features of parathyroid tetany is phosphate retention. Furthermore, tetany has been produced experimentally by feeding phosphates.[5] The phosphate retention in tetany usually is associated with a distinct rise of blood phosphates, the concentration of which partially governs the severity of the symptoms. This is definitely indicated by the observations reported here and by a review of the literature. Pronounced mitigation of symptoms accompanying a fall in blood phosphates has been observed, and simultaneously the neuromuscular electrical excitability approaches normal.

Calcium phosphate is a relatively insoluble compound. It has been stated that the blood is supersaturated with this salt.[6] This has been questioned,[7, 8] but it is certain that it approaches the saturation level. Under these conditions, it might be expected that a decrease in blood phosphates would result in an increase in serum calcium.[9] It has been observed more frequently in these studies, however, that there is a slight fall in total serum calcium accompanying the fall in blood phosphates. It is possible that the relief of symptoms associated with this fall in phosphates is the result of an increase in the percentage of calcium ionized. It is also possible that the decrease in phosphates independently decreases neuromuscular excitability.

RELATION OF CARBOHYDRATES TO BLOOD PHOSPHATES

At the beginning of this century it was generally accepted that phosphate metabolism was not normal in diabetes mellitus. [10, 11, 12] Since that time intensive study has demonstrated an extraordinarily close relationship between carbohydrate and phosphate metabolism. Harrop and Benedict[13] showed that in normal glucose-tolerance curves, the level of blood phosphate fell, the low point of the phosphate curve being subsequent to the highest glucose level. They believed that phosphates are utilized temporarily during the transference of glucose from the blood. This has been corroborated by many writers.[14, 15, 16]

It has been shown that in dogs suffering from tetany, the symptoms are more pronounced on a meat than on a carbohydrate diet. Dragstedt[17] states that dogs with tetany lived longer when fed milk, white bread, and lactose than the usual survival period for thyroparathyroidectomized dogs. In spite of insufficient evidence, his conclusions appear to be correct. Blood studies were not made in his series, and the improvement was considered to be the result of changes in the gut. That the Dragstedt diet is beneficial in tetany has received confirmation. Inouye[18] and Frank, Haring and Kühnau[19] also contend that the beneficial effect of lactose is due to

changes in the intestinal tract, since parenteral administration is not effective. This conclusion is not completely justifiable for lactose is not absorbed as such, but is first hydrolized, with the formation of glucose and galactose. Hydrolysis takes place only to a small extent, however, if the lactose is given intravenously.[20]

Dragstedt believed that benefit was obtained in tetany by a diet of white bread, milk, and lactose because this diet prevented the absorption of toxic substances. Salvasen[3] criticizes Dragstedt's work, and in an excellent treatise presents evidence to prove that the entire benefit of milk is produced by its calcium content. He makes little comment on the effect of milk on blood phosphates. Although there is no question that calcium is essential, the studies herein reported make it apparent that the efficacy of this diet is partly attributable to its effect on phosphate metabolism.

In studying carbohydrate metabolism in parathyroidectomized dogs, Reed[21] found that not only ingestion but also injection of dextrose tends to alleviate symptoms of tetany, causing a decrease in inorganic phosphates and a less pronounced decrease in calcium.

THE OBJECT OF THE STUDY

From the preceding statements it is apparent that an increase in the level of inorganic phosphates in the blood may be closely associated with the production of symptoms in tetany. A fall in inorganic phosphates may cause alleviation of symptoms, even though it is not accompanied by a rise in serum calcium.

The object of this study was to find therapeutic measures which would lower the abnormally high level of blood phosphates, with the expectation that clinical improvement of the patient would result. Since there is such an intimate relationship between carbohydrate and phosphate metabolism, it seemed possible that the level of blood phosphates in tetany might be governed by the proper regulation of carbohydrate assimilation.

EFFECT OF GLUCOSE ON BLOOD PHOSPHATES IN NORMAL INDIVIDUALS

In Table I and Chart I are given results which confirm the finding that inorganic phosphate disappears from the blood after the administration of glucose in normal individuals.

The technic employed is as follows: A specimen of venous blood was obtained after the patient had been without food for twelve to fourteen hours. One hundred grams of glucose were fed, and samples of venous blood were obtained at intervals of half an hour and one, two, three, and four hours, respectively, after the ad-
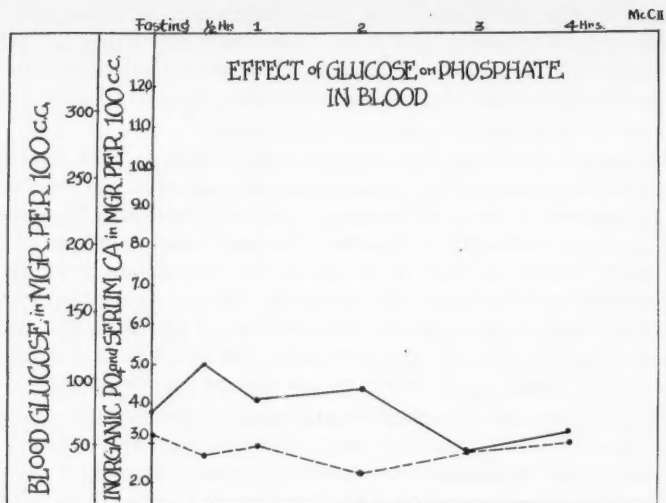
Chart I

TABLE I

Effect of Glucose on Normal Individuals

Time in Hours	Fasting	½	1	2	3	4
Case 1 Sugar, mg. per 100 c.c. whole blood.	83	155	154	119	52	75
Phosphate, mg. per 100 c.c. whole blood.	3.22	2.77	3.09	2.40	2.21	3.25
Case 2 Sugar, mg. per 100 c.c. whole blood.	79	86	111	63	54	53
Phosphate, mg. per 100 c.c. whole blood.	3.64	3.07	3.31	2.58	2.31	2.78
Case 3 Sugar, mg. per 100 c.c. whole blood.	99	113	115	88	90	90
Phosphate, mg. per 100 c.c. whole blood.	3.28	2.23	2.57	2.25	2.34	2.50

ministration of the glucose. Blood sugar and phosphate estimations were made on each sample of blood. Blood sugar was estimated by the method of Hagedorn and Jensen.[22] Phosphates were measured by the colorimetric procedure of Kuttner and Cohen[23] (Table I, Chart I).

An examination of these results demonstrates that the lowest point on the phosphate curve usually appears later than the highest point of the sugar curve. Not infrequently the phosphates return to the normal fasting level before the end of four hours.

Effect of Glucose on Blood Phosphate, Serum Calcium, and Neuromuscular Excitability in Chronic Parathyroid Tetany

The method used was the same as that described above, with the following additions:

Serum calcium determinations according to the Clark and Collip[24] modification of the Kramer and Tisdall method were made on the fasting specimen and on two of the other specimens. The electrical neuromuscular excitability (Erb's sign) was measured immediately before obtaining each specimen of blood. The procedure was as follows:

One of the patient's hands was placed on a large moist electrode connected to the anode of a circuit through which a variable direct current could be passed. The cathode consisted of a small metallic terminal covered with wet chamois. The skin over the median nerve at the wrist on the opposite side was moistened, and the electrode was applied. The circuit could be closed or opened by means of a small switch near the cathode. The amount of current running through the circuit was read from a milliammeter. In each case the current was gradually increased until a point was reached when, on closing the switch leading to the cathode, a contraction could be noted in the hand. The number of milliamperes necessary to produce the contraction was called the cathode closing contrac-
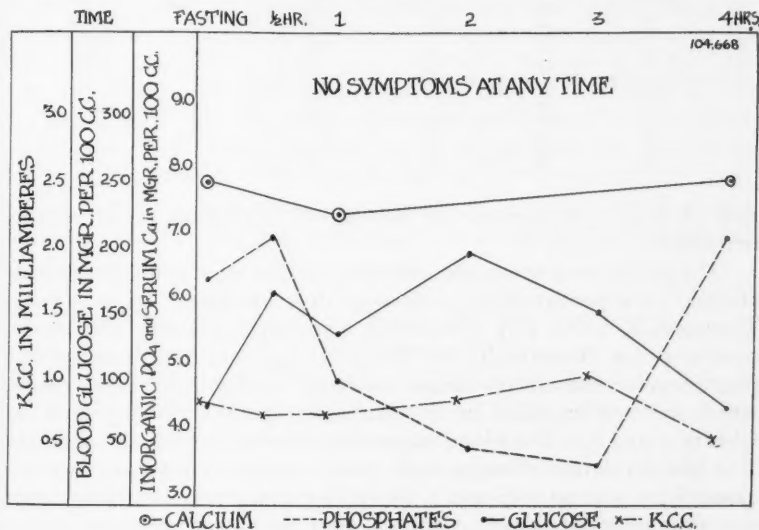

Chart 2

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TABLE II

Effects of Glucose on Chronic Tetany

Time in Hours	Sugar Mg. per 100 c.c. Whole Blood	Calcium Mg. per 100 c.c. Serum	Phosphate Mg. per 100 c.c. Whole Blood	Cathode Closing Contraction	Symptoms
Case 1,					
Fasting	71	4.8	5.21	1.6	Present
½	133	—	4.74	1.6	Present
1	161	5.8	4.74	1.8	Improved
2	126	—	4.21	1.9	Improved
3	61	—	4.16	1.6	Present
4	59	4.8	4.87	1.4	Present
Case 2,					
Fasting	65	6.8	6.50	0.8	Present
½	120	—	4.05	0.8	Present
1	87	6.8	5.30	0.7	Improved
2	87	—	3.60	0.8	Improved
3	58	—	3.00	0.7	Present
4	52	6.8	4.70	0.6	Present
Case 3,					
Fasting	82	7.7	4.07	1.7	
½	142	—	3.30	1.9	
1	182	7.3	3.66	1.9	No definite
2	158	—	2.88	1.8	symptoms
3	117	—	2.42	1.8	
4	76	7.3	2.42	1.7	
Case 4,					
Fasting	79	8.2	4.70	0.7	Present
½	154	—	4.70	1.2	Present
1	134	9.2	4.00	0.8	Improved
2	109	—	4.10	0.7	Improved
3	70	—	4.40	0.7	Present
4	54	8.2	4.10	0.7	Present
Case 5,					
Fasting	83	7.8	5.50	1.6	Present
½	155	—	5.70	1.4	Symptoms better
1	129	7.3	4.80	1.1	
2	111	—	3.30	0.9	
3	68	—	3.45	1.1	Present
4	71	7.3	3.48	1.4	Present
Case 6,					
Fasting	67	6.3	4.80	0.6	Present
½	81	—	5.60	0.7	
1	98	6.8	4.00	—	Gradual
2	89	—	3.20	0.6	Improve-
3	70	—	3.75	0.5	ment
4	70	—	3.75	0.4	Present
Case 7 (Control, no glucose given), No. 223213					
Fasting	73	7.3	6.82	0.9	
½	75	—	6.40	1.0	
1	79	7.3	7.50	1.0	
2	77	—	6.40	0.5	
3	72	—	6.82	0.7	
4	70	7.3	6.40	0.6	

tion (K.C.C.). A decrease in this figure represents an increased irritability.

The patients on whom the following studies were made developed chronic parathyroid tetany following thyroidectomy. In each case Trousseau's, Erb's and Chvostek's signs were present, the latter only at times. Abnormally low blood calcium and high blood phosphate levels were always found, as shown in Table II. (Two cases which are not included in the tables are graphically depicted in Charts 2 and 3.) The blood sugar curves were essentially normal. The blood calcium changes were small and not constant. In four cases there was an increase, followed by a decrease. In two, there was a decrease which persisted until after the end of the experiment. In one case a decrease was followed by an increase, and in one
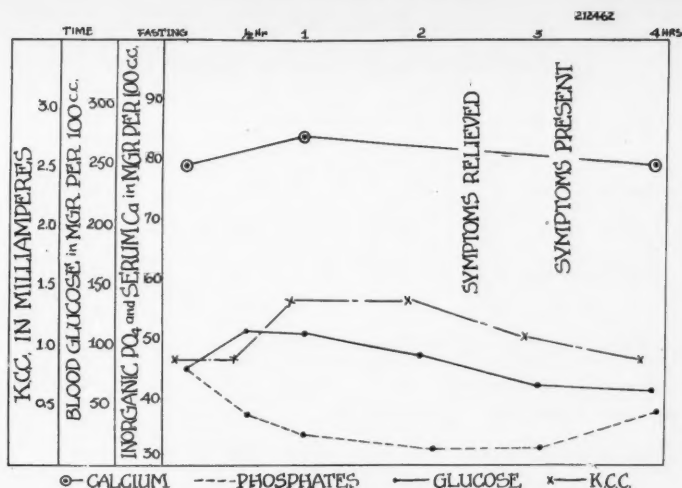
Chart 3

there was no change. The phosphates invariably were decreased. Only in Case 3 did the decrease continue for as much as four hours. This was associated with a more prolonged rise in the blood sugar than in any of the other cases. The neuromuscular excitability showed an almost constant tendency to decrease during the test. Only in Case 5 was there a definite increase in excitability. In all cases in which there were symptoms at the beginning of the test the symptoms were definitely improved during the test, but increased in severity at the end of the experiment when the phosphate level rose. Apparently the symptoms paralleled the phosphate curve more than that of the serum calcium.

In Case 7 no glucose was administered. The results were included to show that the changes recorded in the other tables were caused by the glucose.

Effect of Lactose on Blood Calcium and Phosphate in Normal Dogs

In one of the following sections it is shown that lactose is of great benefit in the treatment of tetany. The effect of feeding lactose to healthy dogs has been compared with the effect of feeding glucose to the same animals. The methods used were the same as those employed for glucose-tolerance tests. The results are shown in Table III. In this table, the blood sugar is expressed in terms of milligrams of glucose. The curve is very different after lactose

TABLE III

Effect of Lactose and Glucose in Normal Dogs

Dog No. 1, Weight 38, Experiment No. 1, Effect of Glucose, Dose 15 Grams

Time in Hours	Fasting	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	92	101	132	95	92	84	—
Phosphate mg. per 100 c.c. whole blood	2.39	2.27	—	2.12	2.32	2.39	—
Calcium mg. per 100 c.c. whole blood	11	—	—	—	—	10	—

Dog No. 1, Weight 38, Experiment No. 2, Effect of Lactose, Dose 15 Grams

Time in Hours	Fasting	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	77	74	117	75	66	75	—
Phosphate mg. per 100 c.c. whole blood	3.11	2.80	2.87	2.96	3.35	3.30	—
Calcium mg. per 100 c.c. whole blood	12.0	—	—	12.1	—	—	—

Dog. No. 2, Weight 55, Experiment No. 1, Effect of Glucose, Dose 20 Grams

Time in Hours	Fasting	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	77	90	119	77	74	72	—
Phosphate mg. per 100 c.c. whole blood	2.82	2.06	2.34	2.61	3.41	3.35	—
Calcium mg. per 100 c.c. whole blood	—	—	—	—	—	—	—

Dog No. 2, Weight 55, Experiment No. 2, Effect of Lactose, Dose 20 Grams

Time in Hours	Fasting	½	1	2	3	4	5
Sugar mg. per 100 c.c. whole blood	79	79	79	75	81	81	79
Phosphate mg. per 100 c.c. whole blood	3.30	2.77	2.84	2.69	2.84	3.03	3.27
Calcium mg. per 100 c.c. whole blood	8.7	—	8.4	—	8.8	—	—

feeding from that exhibited after glucose feeding. The glucose curves are similar to those in normal individuals; the lactose curves are very low, and indicate either a very high tolerance or very poor absorption. The serum calcium does not show a marked or regular change. There is no difference between the type of phosphate curve obtained with the two sugars, and no indication that lactose produces any prolonged depression of inorganic phosphate in the blood.

THE EFFECT of LACTOSE
IN TETANY

138,828

KCC x—   PHOSPHATES•----   GLUCOSE. •—

Chart 4

THE EFFECT OF LACTOSE
IN TETANY
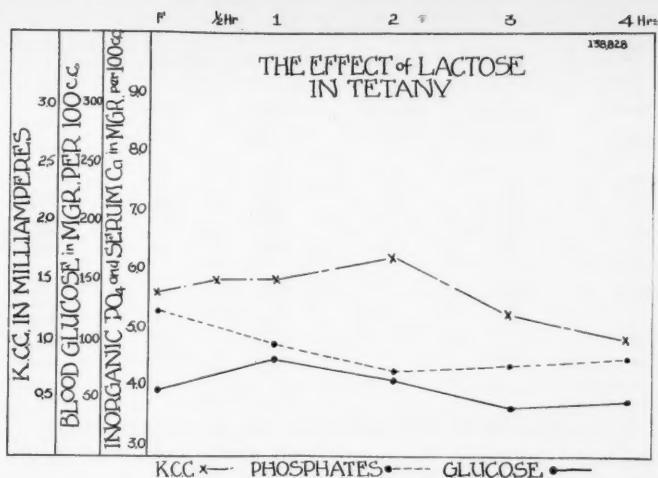
123,527

⊚CALCIUM   •----PHOSPHATES   •—GLUCOSE.   x—K.CC.
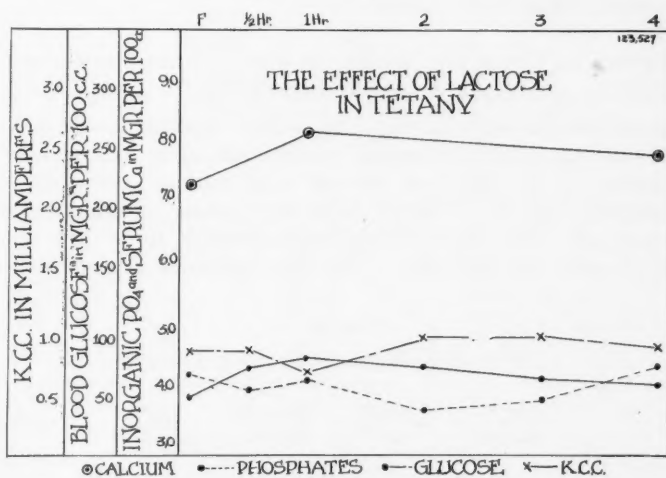
Chart 5

Effect of Lactose in Chronic Tetany

One hundred grams of lactose were administered to each of four patients suffering from chronic parathyroid tetany. The results are presented in Table IV and Charts 4 and 5. The blood glucose curves are of the same general type as those secured after the administration of glucose to normal individuals. The sugar values tend to be

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TABLE IV
Effect of Lactose in Chronic Tetany

Time in Hours	Sugar Mg. per 100 c.c. Whole Blood	Calcium Mg. per 100 c.c. Serum	Phosphate Mg. per 100 c.c. Whole Blood	Cathode Closing Contraction	Symptoms
Case 8					
Fasting	77	7.7	5.00	0.7	Present
½	120	—	4.16	0.9	Present
1	117	7.2	4.16	0.7	Present
2	92	—	3.95	0.8	Improved
3	70	—	3.75	0.8	Improved
4	66	7.2	3.60	0.8	Improved
Case 9					
Fasting	65		3.85	1.0	Present
½	101		2.90	1.5	Present
1	77		3.56	1.4	Improved
2	77		3.56	1.8	Improved
3	48		3.82	1.1	Present
4	61		3.74	1.0	Present

low. Again there is no definite effect on the serum calcium. The depression of inorganic phosphate is about the same as after glucose administration. It appears probable that the lactose is readily digested, with the formation of glucose and galactose, and that absorption takes place rapidly.

EFFECT OF GALACTOSE ON BLOOD CALCIUM AND PHOSPHATE IN A NORMAL INDIVIDUAL

Since the glucose resulting from lactose digestion could account for all the changes in inorganic metabolism after lactose feeding, the effect of the galactose moiety was studied separately. The method was the same except that fifty grams of galactose were administered orally. It was considered advisable to use this smaller dose of galactose because of the low tolerance shown by most

TABLE V
Effect of Galactose in Chronic Tetany

Time in Hours	Sugar Mg. per 100 c.c. Whole Blood	Calcium Mg. per 100 c.c. Serum	Phosphate Mg. per 100 c.c. Whole Blood	Cathode Closing Contraction	Symptoms
Case 1					
Fasting	83	7.2	3.76	1.5	No definite
½	95	—	3.66	1.8	change in
1	104	6.2	3.59	1.8	symptoms
2	97	—	3.68	1.7	
3	90	—	3.68	1.8	
4	83	7.6	3.81	1.8	
Case 2					
Fasting	65	7.8	4.45	0.9	No definite
½	117	—	3.66	0.9	change in
1	95	7.9	3.55	1.0	symptoms
2	102	—	3.57	1.0	
3	83	—	3.64	0.9	
4	75	7.3	3.61	1.0	

EFFECT OF GALACTOSE ON BLOOD PHOSPHATE. Mc C1
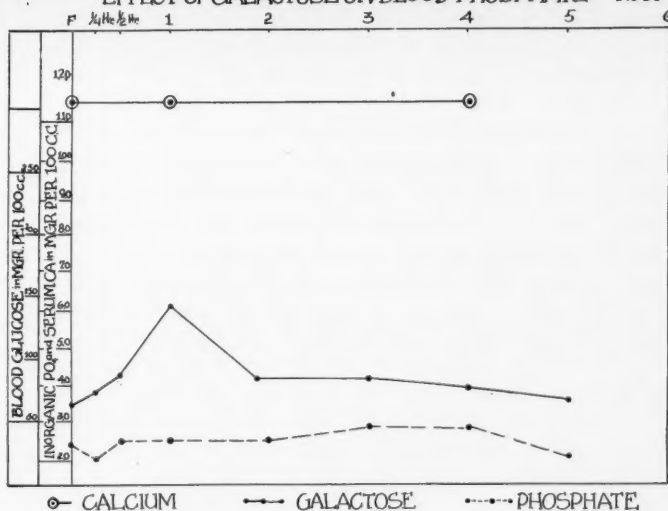
Chart 6

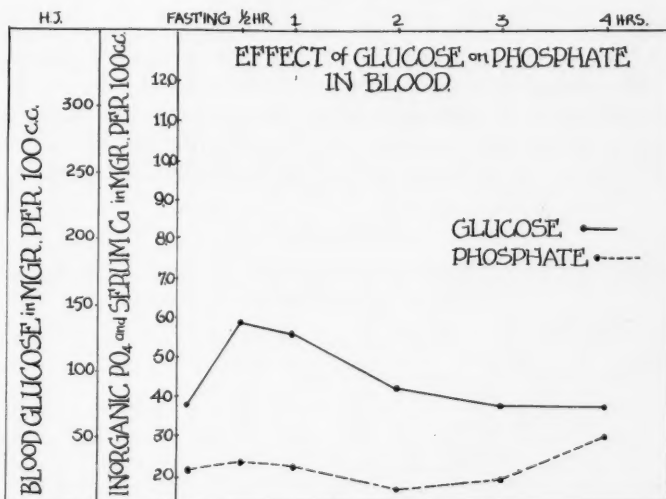EFFECT of GLUCOSE on PHOSPHATE IN BLOOD.

Chart 7

individuals to this sugar. In the following cases, sugar was excreted in the urine. The results are shown in Table V and Chart 6. As a control experiment, 100 grams of glucose were administered to the

same individual (Chart 7). The effect of galactose on blood phosphate is in sharp contrast to that of glucose. This is in accord with the results of Barrenscheen. Galactose does not produce a depression of the phosphate level in the blood.

EFFECT OF GALACTOSE IN CHRONIC TETANY

Galactose was administered also to two patients suffering from chronic parathyroid tetany, with the result summarized in Table V. Evidently there is no difference between the reaction to galactose of normal individuals and of those with chronic tetany. No constant changes in inorganic metabolism appear following the administration of this sugar, the neuromuscular irritability does not show changes corresponding to those which occur after the administration of glucose, and the symptoms are not relieved during the test. Thus it seems improbable that it is the galactose moiety of the lactose molecule which results in depression of the blood phosphate. Further studies concerning the mechanism of the action of lactose on blood phosphate are in progress.

EFFECT OF GLUCOSE, LACTOSE, AND GALACTOSE ON URINE PHOSPHATE EXCRETION

The fate of the inorganic phosphate which disappears from the blood stream has been considered, and it has been demonstrated that this phosphate is not excreted in the urine. In fact, when the blood phosphate is depressed after glucose or lactose administration, the phosphate excretion in the urine diminishes. After the administration of galactose, no definite change develops in the

TABLE VI

Effect of Glucose, Lactose, and Galactose on Urine Phosphate Excretion

(a) In normal individuals

Case No.	Dosage	1 Hour	2 Hours	3 Hours	4 Hours
1	Glucose, 100 gm.	43.8	38.8	29.8	10.5
2	Glucose, 100 gm.	65.9	66.2	58.3	39.6
3	Glucose, 100 gm.	33.3	12.3	0.78	1.05
4	Glucose 100 gm.	32.1	1.16	1.65	0.95
5	Galactose, 50 gm.	33.2	12.9	27.3	21.0

b) In chronic tetany

6	Lactose, 100 gm.	42.8	45.1	5.9	3.0
7	Lactose, 100 gm.	21.3	5.2	20.2	1.5
8	Lactose, 100 gm.	14.7	20.8	10.8	3.9
9	Lactose, 100 gm.	22.1	17.1	4.9	13.8
10	Galactose, 50 gm.	—	37.7	15.9	28.7
11	Galactose, 50 gm	5.2	5.7	4.0	5.4

rate of phosphate excretion. This is to be expected, since galactose does not affect the phosphates in the blood stream. There is no difference between the reaction of normal individuals and those with chronic tetany. The results are given in Table VI. Since the urine specimens were not taken with a catheter, the results given in this table are only approximations. The changes, however, are very marked and regular. It seems probable, from this work, that the phosphates which disappear from the blood are carried into the tissues.

Lactose in the Treatment of Chronic Parathyroid Tetany

In the following cases all calcium and phosphate estimations were made from samples of blood taken after the patient had fasted for approximately twelve hours.

Case 1. A young woman eighteen years of age underwent thyroidectony for adenoma of the thyroid in January, 1921. Two months after the operation she complained of paresthesia and stiffness of the fingers in attacks lasting from a few minutes to a few days. These symptoms persisted. She was treated by oral administration of calcium lactate at irregular intervals. On February 2, 1929, she complained of having had two severe tetanic convulsions. Examination showed the presence of Chvostek's and Trousseau's signs, and the serum calcium was 5.8 mg. per 100 c.c.
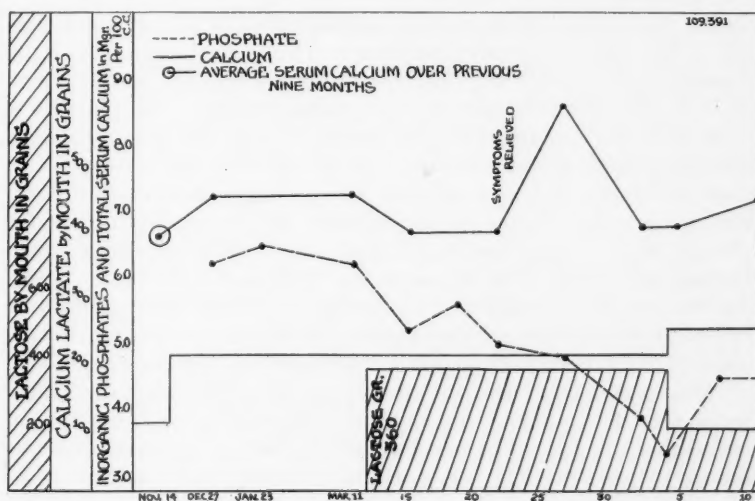

Chart 8

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From this date, 100 grains of calcium lactate were given daily. The symptoms were partially relieved, but mild symptoms continued.

Chart 8 shows that the average serum calcium level, taken at monthly intervals for a period of nine months previous to November 14, 1929, was 6.6 mg. per 100 c.c. On November 14 the daily dose of calcium lactate was increased to 200 grains. The symptoms were improved slightly, and the serum calcium had risen to 7.2 mg. per 100 c.c. on December 27. On this date the inorganic phosphates were estimated for the first time, and were found to amount to 6.2 mg. per 100 c.c.

On January 23 the patient was placed on a high carbohydrate diet containing no meat, eggs, or cheese. In the hope of lowering the phosphate level, extra nourishment, consisting of candy, cake, biscuits, or fruit juices, was advised between meals and at bedtime. Between January 23 and March 11, she had five severe attacks of tetany, the symptoms always being more noticeable in the morning on wakening. Mild symptoms persisted between severe attacks, and the blood chemistry remained approximately the same.

On March 12, 1930, 360 grains of lactose per day were prescribed in addition to 200 grains of calcium lactate as before. These substances were divided into three doses, given before meals. The characteristic change in the chart consists in a persistent fall of the phosphate level. The symptoms were gradually alleviated and finally disappeared on March 27.

On April 4 the blood phosphates had fallen to a level which was lower than that considered necessary. The serum calcium was not normal, and therefore the dose of lactose was reduced to 180 grains and the calcium increased to 240 grains per day. The phosphate level rose, but remained within normal limits. The serum calcium also apparently rose somewhat. The temporary rise of serum calcium on March 27 is unexplained. The average serum calcium level was not greatly affected by the addition of lactose, and except for the one high value, there was a slight lowering of this figure until the calcium intake was increased on April 4. Since March 27 the patient has been completely symptom-free, with the exception of two days when she voluntarily discontinued treatment. On May 8 she stated that she was feeling better than she had for years.

Case 2. A woman, thirty-four years of age, underwent thyroidectomy for adenomata of the thyroid with tracheal compression on November 21, 1929. The basal metabolic rate before operation was minus 16 per cent. On the morning following operation she complained of tingling in the fingers. Her serum calcium on this day was 8.6 mg. per 100 c.c.

At first the patient received calcium gluconate one dram three times a day, and calcium lactate, 20 grains three times a day. Her symptoms demanded the administration of parathormone (parathyroid extract — Collip) on three occasions during the first thirteen days after operation, during which period the blood calcium fell to 7.7 mg. On December 4 the treatment was changed to one dram of calcium carbonate three times a day before meals. The symptoms were lessened in severity and the blood calcium rose from 7.7 mg. to 8.7 mg. on December 9, and to 9.2 mg. on December 12.

This treatment was continued, and the patient was not again observed until she returned on March 5, complaining that she had experienced almost daily stiffness and numbness of the fingers and
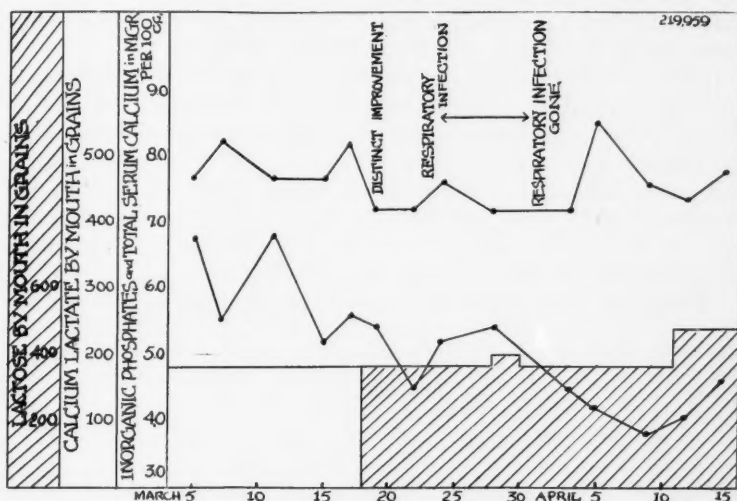

Chart 9

twitching of the facial muscles. The serum calcium was then 7.7 mg. per 100 c.c. and blood phosphates 6.8 mg. as shown at the beginning of Chart 9. The treatment was changed on this date to calcium lactate, 180 grains per day, given in three doses of one dram each before meals. The serum calcium changed very little and the blood phosphate varied between 6.8 mg. and 5.2 mg. per 100 c.c. There were mild symptoms daily.

On March 18 the administration of lactose was started in doses of two drams three times a day before each meal. On the first day there was no improvement. On the second day the symptoms had disappeared, and on March 22 the blood phosphate was 4.5 mg. and

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the serum calcium 7.2 mg. On March 23 she developed a mild infection of the upper respiratory tract, associated with aching pains in the back and limbs. This lasted until March 30, and was accompanied by a slight rise in the blood phosphate level, but there was no paresthesia of fingers or toes and no stiffness of the fingers. Following March 23 the blood phosphate level continued to fall, and the patient felt entirely well.

It should be noted that while the patient's serum calcium varied slightly around the level of 8 mg. per 100 c.c., she had moderate symptoms of tetany associated with a high blood phosphate. Later when the average serum calcium level was lower, the symptoms were greatly improved, associated with a fall in blood phosphates. It might be mentioned again that the blood phosphate levels given were estimated while the patient was fasting. Probably they were lower during the day than those shown in the chart.

Case 3. A woman aged thirty-two underwent a thyroidectomy for hyperthyroidism on February 20, 1930. Her basal metabolism before operation was plus 49 per cent. About thirty-six hours after the operation she complained of twitching of the facial muscles and paresthesia and stiffness of the fingers. Both Chvostek's and Trousseau's signs were present. The serum calcium on February 22 was 7.2 and on February 24 was 6.7 mg. per 100 c.c. The blood phosphate on this date was 6.2 mg. per 100 c.c.

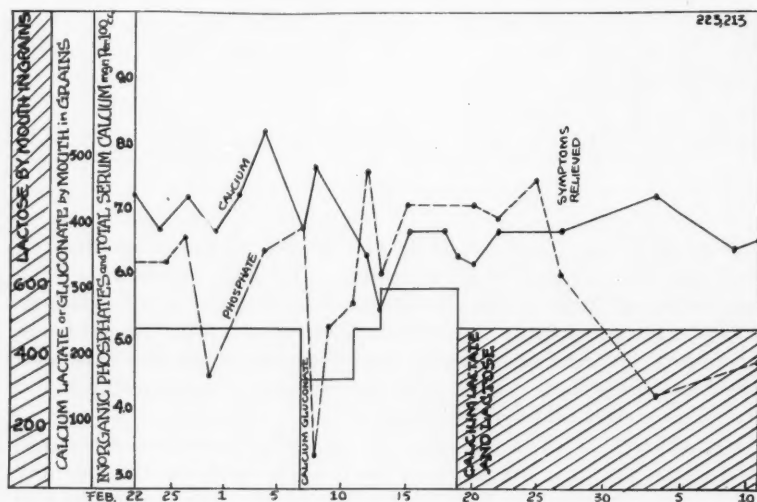Treatment was begun February 22 in the form of calcium lac-

Chart 10

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tate, 240 grains per day, 1 dram before meals and at bedtime, as shown in Chart 10. Symptoms were present daily, and the fasting serum calcium and blood phosphate varied as indicated.

On March 7, calcium lactate was discontinued and calcium gluconate was started, 180 grains per day in doses of 1 dram before each meal. The blood phosphate content fell markedly, but soon rose again to a higher level than before, in spite of the fact that the dose of calcium gluconate was raised first to 240 grains and later to 300 grains per day. The symptoms had disappeared on March 10, but on March 11 they reappeared and were more severe than before. Symptoms were present from the latter date until March 26.

On March 19 the treatment again was changed. The same amount of calcium lactate as was given previous to March 7 was prescribed. In addition to this, lactose was given in amounts of 480 grains per day, two drams being given with one dram of calcium lactate before each meal and at bedtime. For six days no distinct benefit was noted, but on March 27, the eighth day after the administration of lactose was started, there was definite improvement in the severity of the symptoms, accompanied by a fall in blood phosphates but without any rise in serum calcium. On this treatment the blood phosphates fell to a normal level, and symptoms disappeared entirely. The fasting blood phosphates are known to have remained normal for at least one month on this treatment, with the exception of two estimations done within one week following the extraction of an acutely abscessed tooth. On these occasions the phosphates were 6.4 and 6.0 mg., respectively. The patient was known to be symptom-free on May 8, 1930.

It is interesting to note again that the improvement in symptoms was associated with a fall in the level of blood phosphates but not with a distinct rise in the total serum calcium.

Case 4. A woman thirty-four years of age underwent thyroidectomy for adenoma of the thyroid in June, 1923. The second day following this operation tetany developed. She experienced tingling, numbness, and stiffness of the fingers daily, and on occasions had severe generalized convulsions which were thought to be epileptic in character, but as the convulsions have not recurred since she has had adequate treatment for tetany, it is probable that they were caused by this condition.

From June, 1923, to the present time the patient has required constant treatment. At first, when she was taking 10 grains of calcium lactate and 1/10 grain of parathyroid extract twice a day together with a mixture containing sodium bromide and tincture of hyoscyamus, she was not relieved, and continued to have symp-

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toms daily and generalized convulsions occasionally. In May, 1925, when the calcium lactate was increased to 20 grains three times a day, she was somewhat relieved.

In June, 1926, injections of parathyroid extract (Collip) were begun, and a dose of 1 to 2 c.c. was administered subcutaneously every second or third day. In addition to this, she received parathyroid extract, grams 1/5, and calcium lactate, grains 10, three times daily, together with cod liver oil. In October, 1928, the intake of calcium lactate was raised to 120 grains per day. The patient felt better than she had since before the onset of the condition, but as moderately severe symptoms frequently were present, it was still necessary to give parathyroid extract (Collip) in doses of 20 to 40 units (1 to 2 c.c.) on alternate days.

This type of treatment was continued until January, 1930, when the dose of calcium lactate was raised to 360 grains per day. At this time the symptoms, though reduced, were persistent, and the patient began again to take about 2.5 c.c. of parathyroid extract daily. On March 11, 1930, lactose was added in amounts of 360 grains per day, with two drams each of lactose and calcium lactate before meals. The patient became symptom-free, and the parathyroid extract was reduced gradually.

Many important details have been necessarily omitted, but this outline conveys some idea of the severity of the disease in this case and of the type of treatment employed. Serum calcium and blood phosphate levels are not quoted in detail, but from January, 1925, to March, 1930, the serum calcium varied from 6.2 mg. to 9.7 mg. per 100 c.c., according to the treatment used. The most constant figure was between 7 and 8 mg. The blood phosphates in January, 1930, before beginning treatment with lactose, were 6 mg. per 100 c.c.

At the time indicated at the beginning of Chart 11 the patient was receiving 1 c.c. of parathyroid extract (Collip) per day, 300 grains of calcium lactate, and 360 grains of lactose. As she had been symptom-free since beginning the use of lactose, it was decided that the calcium lactate and lactose should be stopped entirely in order to see how much parathyroid extract (Collip) was necessary to relieve the symptoms completely. With the patient's permission and cooperation, on April 9 no calcium or lactose was taken at noon or in the evening, two drams of each being taken before breakfast as usual.

Early in the morning of April 10 symptoms appeared and therefore 2 c.c. of parathormone (parathyroid extract, Collip) were given subcutaneously at 8 a.m. and 4 c.c. at 5 p.m. On April 11 the severity
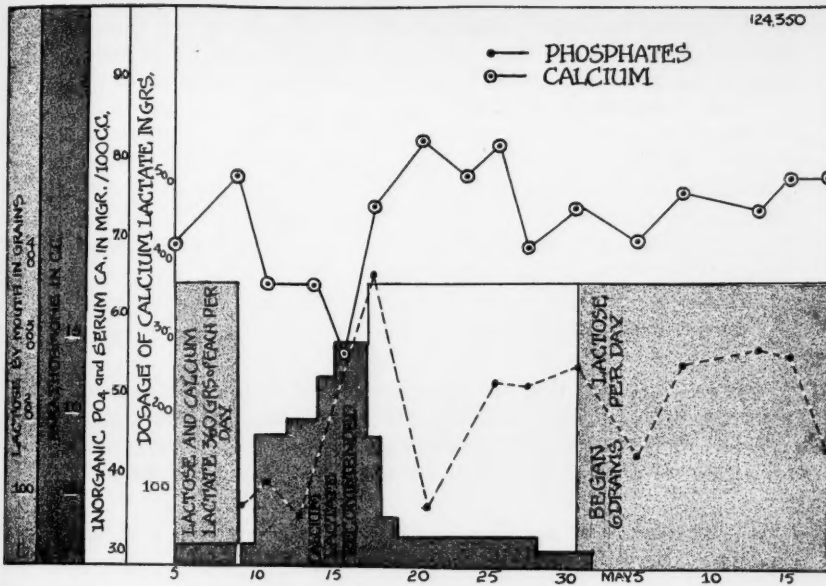
Chart II

of the symptoms increased and 8 c.c. of parathormone were used, 4 c.c. at 8 a.m. and 4 c.c. at 5 p.m. The same dose was given on the following day. The blood calcium apparently was falling, but the phosphates were being held well in check. On April 13, despite the administration of 4 c.c. of parathormone at 8 a.m. and 5 c.c. at 5 p.m. the symptoms were becoming more severe. The fingers were stiff, the patient was nauseated all day and took only small amounts of food with difficulty, and she staggered markedly when she walked. On April 14, 6 c.c. of parathormone were given subcutaneously at 9 a.m. There was slight relief in half an hour, but at 4:30 p.m. the symptoms again became more severe. On April 15, 6 c.c. of parathormone were injected at 8 a.m. and 7 c.c. at 5 p.m. The patient was slightly better on this day, but still had some carpal spasm and nausea. On April 16, the symptoms were severe. The muscles of the arms and legs were becoming sore. Seven c.c. of parathormone were given at 8 a.m. and 6 c.c. at 5 p.m. The report on the blood chemistry showed that the serum calcium had fallen to 5.2 mg. and the phosphate had risen to 4.5 mg. per 100 c.c. Because of this and the severity of the symptoms, calcium lactate was given, 2 drams before dinner and 2 drams at bedtime.

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The following day she again began to take calcium lactate, 360 grains per day. The serum calcium rose promptly and the symptoms were completely relieved. The parathormone was reduced to 2 c.c. per day. Since slight symptoms were present, the dosage of parathormone was not decreased until April 28. The symptoms from April 17 to May 1 were very slight, but not mild enough for the parathormone to be discontinued. On May 2, 360 grams of lactose were given, divided into three doses, before meals, in addition to the same dosage of calcium lactate as before. The patient was instructed to use parathormone as before, when required for the relief of symptoms. Up to May 8, she had not found it necessary to use any injections, as there had been no paresthesia or stiffness of the fingers since administration of lactose was started.

It was expected that the phosphate level would rise somewhat after the discontinuance of the parathormone, and this has occurred. The patient has noticed very mild symptoms on two days, but they have been so slight that up to the present time she has preferred not to use parathormone.

The patient was last seen on May 20, when she was practically symptom-free.

Discussion

In chronic tetany, definite improvement in symptoms apparently results from the feeding of lactose. This is associated with a fall in the level of inorganic phosphates in the blood. During glucose assimilation after the ingestion of glucose or other carbohydrates, there is always temporary improvement in symptoms, associated with a fall in the phosphate level. Nevertheless, even frequent carbohydrate feedings do not result in the permanent benefit which is observed after the administration of lactose. After single doses of glucose or lactose the blood phosphate returns to the previous level within four hours. It seems remarkable that when lactose is used therapeutically, low levels of inorganic phosphate can be demonstrated in the blood twelve to fourteen hours after the last dose of lactose is taken.

The complete mechanism of the action of lactose on blood phosphates is obscure. At first it was thought that the slow digestion of lactose, and the resulting slow absorption of glucose and galactose, might account for the prolonged depression in the phosphate level in the blood. After examination of the blood following the oral administration of one dose of lactose this seems unlikely. The blood sugar level rises sharply and falls again within four hours, indicating rapid absorption and assimilation. The inorganic phosphates also return to a normal level within this period. The feces have not been

examined quantitatively, but it has been shown that the phosphate depression is not the result of increased urinary excretion. On the contrary, there is a retention of urinary phosphates after the administration of single doses of lactose.

The possibility that galactose might have a specific effect was considered. It is known that glucose can be formed in the body from galactose which has been absorbed from the intestine. If the glucose, so formed, is assimilated in the same manner as ingested glucose, it was thought that an extended period of carbohydrate assimilation might result. This in turn would cause a prolonged depression of the phosphate level which would simulate the long, low phosphate curve noted after the administration of glucose to diabetics, when assimilation of the glucose is delayed.

At present, the data concerning this point are insufficient to warrant definite conclusions. Our results, however, and those of Barrenscheen[25] fail to demonstrate any connection between the metabolism of galactose and that of inorganic phosphate in the blood. The use of galactose over long periods may cause us to draw different conclusions. As yet, there is no definite evidence that the efficacy of lactose is due to changes in intermediary metabolic processes. It may be that there is a slowing of the absorption or an acceleration of the excretion of the phosphates.

Neither Dragstedt[17] nor his recent supporter, Hutton,[27] have associated the effect of lactose with mineral metabolism. Those who believed that parathyroid tetany was caused by changes in calcium metabolism were of the opinion that lactose produced an increased absorption of calcium by the production of acidity in the gut.[26] So far as we are aware, no one has demonstrated an increased blood calcium after lactose administration. Since calcium phosphate is very insoluble, it is possible that an increased absorption of calcium might result in a lowering of the phosphate level due to a deposition of calcium phosphate in the tissues. Hence, increased calcium absorption might not be apparent on examination of the blood.

Summary and Conclusions

1. The symptoms of chronic parathyroid tetany may be lessened in severity or completely controlled by lowering of the amount of inorganic phosphates in the blood without raising the total calcium content of the blood serum.

2. Glucose temporarily lowers the amount of inorganic phosphates in the blood of normal subjects and in individuals with chronic parathyroid tetany.

3. Lactose in single doses has the same effect as glucose.

4. Galactose in single doses has no effect on the inorganic phosphate content of the blood.

5. After ingestion of glucose or of lactose there is a decrease in the amount of phosphate excreted in the urine. This does not occur after the administration of galactose.

6. Three cases of chronic parathyroid tetany are reported in which symptoms were present in spite of the oral administration of large doses of calcium lactate. The addition of lactose resulted in complete relief, associated with a lowering of the phosphate content of the blood.

7. One case of chronic parathyroid tetany is reported in which large doses of calcium lactate alone failed to give complete relief and very large doses of parathyroid extract (Collip) alone failed to give relief. The symptoms could be controlled by the oral administration of large doses of calcium lactate, together with the subcutaneous injection of parathyroid extract. Calcium lactate in large doses in combination with lactose gave relief without the addition of parathyroid extract.

8. The mechanism of the action of carbohydrates in lowering the amount of phosphates in the blood is discussed.

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EDEMA DUE TO VITAMIN "B" DEFICIENCY

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"B" avitaminosis is a deficiency disease of unusual interest and infrequent occurrence in this country. Following is the report of such a case in a patient, who suddenly developed generalized edema, following a prolonged reducing diet, deficient in vitamin "B."

The patient, a lawyer, aged 27, was seen first in the Cleveland Clinic, on February 6, 1932. Medical advice was sought because of sudden increase in weight, accompanied by swelling of the face and legs. The illness had begun one week before admission when the patient first had noticed a swelling of his abdomen and legs which had appeared rather suddenly. The patient found that he had gained eleven pounds in weight over a period of three days; at the end of a week he had gained sixteen pounds. The swelling increased in proportion to the increasing weight, and always was worse in the mornings, tending to decrease towards mid-day. On several occasions the patient had awakened in the morning with his eyes swollen completely shut. His only other complaints were of a feeling of discomfort in the lower chest and upper abdominal region, of some weakness and of loss of "pep". There were no genito-urinary symptoms until about two days before his admission when he had noted some frequency and since then had been voiding an unusually large quantity of urine.

On questioning the patient it was found that he had been on a very restricted, poorly balanced diet for the last year and a half. In January, 1930, numerous furuncles, scattered over his entire body had developed. These had proved very resistant to treatment and his physician finally had advised a diet in which starches, sugars and fruits were prescribed. The patient had existed on a grapefruit and a small portion of meat (beef) each day with a little lettuce once or twice a week. After dieting in this manner for about six weeks, the boils had disappeared and the patient had lost about 25 pounds in weight. He felt so much better with his weight reduced, that he decided to continue on this diet, which he carried out with very little variance for a total period of a year and a half. After dieting for a few months, he soon lost his appetite and had no desire for food. During the entire period his weight had been reduced from 165 pounds to 105 pounds. His weight was maintained for three to four months at 105 to 110 pounds, when edema supervened.

The patient weighed 127 pounds and his height was 5 feet, 3 inches. The skin and mucous membranes appeared healthy. The ·eye examination revealed nothing abnormal; the tonsils had been removed and there was no evidence of oral sepsis. The thyroid was not enlarged and there were no palpable glands in the neck. There was a general puffy appearance of the face, most marked in the tissues around the eyes. The chest was symmetrical, the lungs clear, and no pleural effusion could be demonstrated. The heart seemed normal in size and no murmurs nor arhythmia could be demonstrated. The skin over the pectoral region was very loose and edematous; palpation showed the existence of pockets of fluid between the chest wall and the underlying subcutaneous tissues. There was diffuse edema of the abdominal wall similar to that found in the chest. There was no evidence of ascites. The external genitalia were entirely normal, without any evidence of edema. The legs, ankles and feet showed a moderate amount of edema which pitted deeply on pressure. All superficial and deep reflexes were normal. There was no evidence of arteriosclerosis. No muscular atrophy or weakness could be demonstrated; there were no sensory disturbances, and the Jongkok test was negative.

The pulse rate was 60 and the blood pressure was 100 systolic, 64 diastolic. The blood count showed 4,400,000 erythrocytes, 7,250 leucocytes, and the hemoglobin, 84 per cent. The blood sugar was 77 milligrams per hundred cubic centimeters one hour after a meal. The level of the urea in the blood was 24 milligrams per cent. The results of the urinalysis were negative except for a low specific gravity, 1.010. The Wassermann and Kahn tests were negative.

The information obtained from the physical examination and from the routine laboratory tests was sufficient to rule out the presence of any of the diseases commonly producing edema.

The history of a low caloric intake over a long period of time, which had resulted in marked loss of weight, anorexia and weakness followed by the rather sudden onset of edema, immediately raised the question as to whether or not this might be a case of so-called inanition edema.

It was felt that the condition might easily be a Vitamin B deficiency disease, that is, a wet form of beriberi in which the neuritic symptoms were absent or masked by the edema.

The rather unusual features of the case prompted further studies. The plasma protein, carbon-dioxide-combining power of the plasma, and the inorganic constituents of the blood were checked with the following results:

Serum Proteins	6.74	per cent
Serum Albumin	3.97	per cent
Serum Globulin	2.77	per cent
Euglobulin	0.99	per cent
Pseudo globulin I	0.42	per cent
Pseudo globulin II	0.36	per cent
Cholesterol	150	mg.
Sodium Chloride	577	mg.
Phosphorus	3.5	mg.
Calcium	9.7	mg.
Urea	24.0	mg.
Uric Acid	1.7	mg.
Non-Protein Nitrogen	22.4	
Carbon Dioxide Combining Power	57.6	
Basal Metabolic Rate:		
Dubois	—23	per cent
Sanborn	—26	per cent
(Based on 116½ pounds)		
Phenolsulphonephthalein:		
First hour	30	per cent
Second hour	35	per cent
Urea Clearance	67	per cent function

The plasma proteins in which we were most interested, were entirely within normal limits as were the carbon-dioxide-combining power of plasma and the inorganic constituents of the blood. The basal metabolic rate was rather low but this is to be expected in patients with edema. Roentgenographic studies of the gastrointestinal tract revealed pylorospasm and a very large, atonic colon.

The edema in this case could not be explained on the basis of low osmotic pressure of serum proteins, as is found in inanition edema; and hence it was felt that it must be closely related, if not identical, to the edemas which occur in the wet types of beriberi. Although there were no neuritic symptoms in this case, it has been repeatedly shown that ship beriberi, a wet form of the disease, is a deficiency disease in which nervous phenomena are rarely present and that edema of various degrees is the predominating, oftentimes the only, physical finding.

The patient, thoroughly alarmed about his condition, was quite willing to cooperate, and to dispense with his past dietary regimen. He was given a diet with a high vitamin, and low carbohydrate content, with a supplementary supply of vitamin B in the concentrated form of Vitamin B Extract, Parke, Davis & Co., in doses of two drachms three times daily.

The patient's response to this form of treatment was most satisfactory. The edema disappeared rapidly. In a week he had lost 10 pounds, his appetite had returned to normal, and he felt a "hundred per cent better." The edema had entirely disappeared from his

face, but was still evident in the pectoral region and in the lower extremities. He was advised to continue the treatment and to return at weekly intervals for observation. Edema continued to decrease and there was a gradual loss in weight, so that at the end of three weeks, there was no evidence of any gross edema. He had lost 16 pounds, undoubtedly due to the loss of fluid, in fact the amount of fluid lost was probably even greater than would appear from the figures, as most likely he had gained actually on the more substantial diet. The patient then began to gain, hoping to reach and maintain his weight at a level between 125 and 130 pounds, the proper amount for a man of his stature. Simultaneously with the disappearance of the edema there was a very marked increase in the urinary output. In June, 1932, after having been free from symptoms for four months, the patient returned because of a reappearance of the edema. He had gained 10 pounds rather suddenly and had had a very scanty output of urine. These symptoms occurred while the patient was on a three weeks' business trip, during which time he had stopped taking the Vitamin B Extract. The edema appeared almost two weeks after the extract was discontinued. An analysis of the serum proteins was done at this time and was found to be entirely normal. (Serum proteins, 8.32; albumin, 4.74; globulin, 3.58.) Curiously enough, ten days after treatment with vitamin B was reinstated, the edema had entirely disappeared and the urinary output had returned to normal. The patient has remained well to the present time; however, he still is taking a liberal supply of vitamin B daily along with the proper diet. Subsequent examinations failed to show any evidence of peripheral neuritis. Repeated urine analyses during the period of observation showed no evidence of renal damage.

With the marked amelioration of symptoms and entire disappearance of edema on a high vitamin B diet, without the aid of other therapeutic measures, it was felt that this case was indeed one presenting the clinical picture and course of wet beriberi.

Discussion

In studying this case, inanition edema had to be considered. This symptom complex has been described under various names, among which are: war edema, famine edema, prison dropsy, and nutritional edema. The edema in these cases is of the generalized nephritic type and usually develops in an individual who has become emaciated from a protracted, semi-starvation diet. The condition has been reported as occurring frequently in famines, in prisons, and in asylums. At times it has been so prevalent that the term, epidemic dropsy, has been used to designate the disease. It was com-

mon in certain European countries toward the end of the World War, and studies were made in an attempt to determine its etiology.

Various workers have ascribed the dropsy in inanition edema to a lack of calcium fat and phosphorus in the blood. The importance of fresh vegetables, protein and vitamins has been emphasized.

After studying a large series of cases in 1920, Maver[5] concluded that it is a deficiency disease and is the result of protracted subsistence on a diet deficient in calories, and especially deficient in protein content; undoubtedly a high fluid intake and possibly a high salt intake are important accessory features. In the cases in his series, the edema was the most prominent feature and was most common in the feet and legs, at times extending to the thighs and trunk and in about one-half the cases including the face. Marked muscular weakness and alimentary disturbances were common. The urine was pale, of low specific gravity, but was free from albumin. Characteristic findings in Maver's group of patients were sub-normal temperature, slow pulse rate, low blood pressure, and low basal metabolic rate. They usually recovered after resuming a normal diet and receiving proper hospital care.

Inanition edema occurring in private medical practice has been variously described. Wolferth[12] reported two interesting cases following profound alimentary disturbances due to postoperative fecal fistula, diarrhea and vomiting. His findings were similar to those found in the cases of war edema, but he also found the serum protein content of the blood to be low. Landis and Leopold[4] described a case of edema in a patient with tuberculosis enteritis; special studies showed slight elevation of the capillary blood pressure and a marked diminution of the osmotic pressure of the serum proteins. Blood transfusions were followed by marked subsidence of edema and a rise in the level of the serum protein.

In a more recent study of the serum proteins in a large variety of diseases, Bruckman and Peters[1] stated that non-inflammatory edema which could not be ascribed to cardiac or renal disorders is found only when there is obvious malnutrition. They found that there is no correlation between edema and the concentration of globulin, and that *edema was observed in patients with malnutrition only when serum albumen is below the normal level.* Edema almost invariably develops when the level of serum albumin falls below 3 per cent, is seldom found when the amount of albumin exceeds 4 per cent. These workers concluded that malnutrition edema appears to be referable to a deficiency in serum albumen caused by wastage of body protein as the result of disease or an inadequate diet.

Beriberi is a rare disease today. It is most unusual to see the condition in this country, although a few sporadic cases have been reported. That a diet deficient in vitamin B, if taken for a prolonged period, causes beriberi, is a generally accepted fact. Although vitamin B is quite widespread in the animal and vegetable kingdom, we know that meats, milk and fruit juices contain relatively small amounts of it, and when the diet is otherwise deficient, relatively large amounts of these foods must be consumed in order to prevent the development of beriberi. Vitamin B is found in abundance in whole grain cereals, brewer's yeast, egg yolk, dry prunes, spinach, and the lentils. It is relatively heat stable, but is destroyed in the heat used in sterilization. Vedder,[11] in an excellent monograph on the subject, stated that in sporadic cases some anti-beriberi vitamin usually is ingested, but should the amount be insufficient for normal body metabolism, the patient, after a prolonged depletion period, may develop beriberi in as severe a form as though the diet were strictly vitamin-free. He said that experimental work on scurvy and beriberi has demonstrated the fact that the body is unable to store up any reserve of vitamin, that when a diet deficient in vitamins is adopted, impairment begins at once. Degenerative changes occur in the nerves of fowls within seven days, when they are fed only decorticated rice; however, this impairment does not lead to symptoms at once. The depletion period as shown by various human feeding experiments usually occurs in man within 90 to 120 days. In the case under discussion there were no symptoms for about a year and a half, the patient apparently feeling well until the sudden onset of edema and weakness caused him to seek medical advice.

The cause of edema in beriberi has always been obscure. Mc-Callum[7] expresses the opinion that protein shortage is the probable cause of starvation dropsy and that wet beriberi may be an expression of two specific dietary lacks, protein starvation and deficiency of vitamin B. With the discovery that plasma proteins are reduced in cases of nephrosis and other edemas it was thought that some light might be thrown on the mechanism of the production of edema in beriberi. However, no confirmatory reports are to be found in the literature. Kabayaski[3] reported the serum proteins normal in beriberi while Shigeari and associates[9] observed low values during the edematous stages which rose to normal or above after the disappearance of the edema.

Nakazama and co-workers[8] reported serum albumen values seldom below 4 per cent and colloid osmotic pressure of only 1 per cent below normal. They found the molecular weight of albumen greater in the edematous forms and suggest the hypothesis that

the blood building mechanism is disturbed in beriberi. McCarrison[6] found that the adrenals of fowls suffering from "B" avitaminosis are considerably enlarged, and that the secretion of adrenalin by these enlarged glands is proportionally increased. He suggested that the edema may be due to circulatory changes resulting from this increased secretion of adrenalin. Vedder[11] stated that there is considerable experimental evidence to indicate that two vitamins are deficient in the diet that produces beriberi and suggested the possibility that the deficiency of one, the anti-neuritic vitamin, produces degeneration of the nervous system and the symptoms of dry beriberi, while deficiency of the second vitamin produces generalized edema and the syndrome, wet beriberi. Sargent[9] pointed out that in the wet form of beriberi an affection of the vasomotor nerves produces edema while in the dry form paraplegic manifestations are produced and palsy and atrophy of muscles occur.

The pathologic findings in wet beriberi, to quote the older pathologists are "water here, water there, water, water everywhere." McCarrison[6] reported that all organs suffer atrophy except the adrenals which are hypertrophied. Cameron[2] found hyperemia of the adrenals and hypertrophy of the islands of Langerhans in the pancreas. The peripheral nervous system shows typical Wallerian degeneration. Hypertrophy and dilatation of the heart is present in most cases that come to necropsy.

The treatment of beriberi obviously consists of supplying the patient with the factor missing in his diet, namely, vitamin B. This may be done by an adequate diet rich in vitamins or by supplying the deficient factor in the form of vitamin "B" extracts, wheat germ, or yeasts. The liquid extract is the more palatable of the various products on the market and is particularly potent in the vitamin B[1] (anti-neuritic) factor. The edema usually clears up rapidly with proper treatment. If neuritis is present recovery is much less prompt as regeneration of nervous tissue always is slow.

The prognosis in beriberi is most favorable. Death seldom occurs in cases in which appropriate treatment is administered. The very high percentage of fatalities in some reported instances has occurred in circumstances where the adequate diet could not be administered.

Summary

A young man exhibited generalized edema and weakness following a generally inadequate diet, deficient in vitamin B. Laboratory tests, including a study of the plasma proteins and of the inorganic constituents of the blood were entirely normal. The complete disappearance of the edema and general symptoms, after a course of

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treatment consisting of the administration of vitamin B and an adequate diet, is proof that the condition was a deficiency disease, a B avitaminosis or wet beriberi.

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ENTERO-VESICAL FISTULAE

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The term entero-vesical fistula includes all those cases in which a communication, direct or indirect, exists between the bladder and any portion of the intestinal tract, from the pyloric orifice to the anus. The condition is somewhat rare, as evidenced by a review of the literature. The first attempt to collect and classify these cases was made by Blanquinque in 1870. The older writers considered the condition beyond the reach of "the art," and the first suggestion as to rational treatment was made by Barbier de Melle in 1843. He believed the site of the fistula was always in the cecum and proposed colostomy as a means of cure. Pennell, in 1850, and Curling, in 1852, first used this procedure. However, up to 1870, only six colostomies had been performed for entero-vesical fistula.

In 1870 Simon operated on two patients with recto-vesical fistula, sectioning the rectal sphincter and making a direct suture of the rectal orifice of the fistula. He was successful in one case. Billroth, in the same year, performed this type of operation without success. Dumeni, in 1884, reported a case of recto-vesical fistula before the French Surgical Congress at Rouen, and highly extolled colostomy as a means of relief; it is probably due largely to him that this procedure became popularized. Suprapubic cystotomy and suturing of the bladder orifice of the fistula was first suggested by Le Dentu in 1884. This method was used for a time, but without success. In 1887 Czerny performed the first laparotomy for vesico-intestinal fistula; the operation, however, was unsuccessful. In 1891 Baiffin performed a similar operation with success.

Cripps, in 1884, reported thirteen cases of congenital entero-vesical fistula; in six of these cases the fistula was between the rectum and the prostate; in three, between the rectum and the bladder, and in one, between the distal end of the sigmoid and the bladder. The location was not mentioned in the remaining three.

Chavannaz, in 1897, Pascal, in 1900, and Parham and Hume, in 1909, writing on entero-vesical fistula, made excellent contributions to the subject and brought the literature up to date. Cunningham, in 1915, reviewed the literature and also reported eight cases of his own. G. Albano, writing in 1926, on the subject of entero-vesical fistula, reported 433 cases. He found that 75 per cent occurred in males, and that only 1.79 per cent of these fistulae healed spontaneously.

In reviewing the literature from 1926 to 1931, I have been able to collect but twenty-nine cases, making a total of 462 cases, to

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which is added our series of eleven cases. Only two cases of congenital
fistula have been described since Cripps reported his series, and the
one in the series presented in this paper, makes a total of sixteen
such cases reported in the literature. There is very little mention
made of the congenital fistula by most of the writers on the subject.
(Table 1.)

TABLE 1
ETIOLOGICAL TABLE—259 Cases*

A. Traumatic, 58 cases, 22.4 per cent.

Accident	No. Cases	Per Cent
a. Gunshot	37	63.8
b. Surgical	13	22.4
c. Childbirth	8	13.7

B. Non-traumatic

1. Inflammatory, 138 cases, 53.4 per cent.

	No. Cases	Per Cent
a. Diverticulitis	77	55.8
b. Tuberculosis	26	18.8
c. Lues	5	3.6
d. Appendicitis	11	7.9
e. Diverticulum bladder	3	2.1
f. Typhoid	2	1.4
g. Actinomycosis	3	2.1
h. Vesical calculus	11	7.9

2. Tumors, 58 cases, 20.1 per cent.

Malignant	No. Cases	Per Cent
a. Carcinoma rectum	14	26.8
b. Carcinoma sigmoid	11	21.1
c. Carcinoma bladder	6	11.5
d. Carcinoma uterus	7	13.4
e. Carcinoma, site not given	15	28.8

3. Congenital, 10 cases, 3.9 per cent.

*Table based on cases collected from the literature.

The above table shows the etiologic factor in 259 cases of entero-
vesical fistulae. Gunshot wounds were the cause of the fistu'ae in
most of the cases classified as of traumatic origin. There had been a
decrease in this variety in the past twenty years. Sutton found only
one case due to bullet wounds in his series of thirty-four cases in
which operation was done at the Mayo Clinic between January 1,
1907, and January 1, 1920. There was none in our series, and no
reference to such cases was found from 1927 to 1931.

Trauma inflicted during surgical operation is the next most
common cause in this group, as in Case II, where a fistula developed
two weeks after a pelvic laparotomy which had been performed else-

where. Sutton reported one case in which the colon was nicked at operation. J. H. Morrisy reported a case in which two loops of the ileum were caught in the suture while a vaginal suspension of the uterus was being done. The patient developed an ileovesical fistula and died. Kustner reported a case which followed the removal of a dermoid cyst. The majority of the other cases were due to operations for removal of stones from the bladder through the urethra, and occurred before the advent of the modern cystoscope. Eight cases were reported as due to childbirth.

In the non-traumatic group the inflammatory lesions constitute the greatest proportion and heading the list of these is diverticulitis. This is considered by some observers to be the most common cause of vesico-sigmoidal fistula. It formed 29 per cent of the above series. In Sutton's series it formed 17.64 per cent. In a series of forty-two cases collected by Bryan twenty-two (52.28 per cent) were due to diverticulitis of the sigmoid. In our series two (18.18 per cent) were due to diverticulitis of the sigmoid.

The etiology of diverticula of the large bowel is still obscure. Chute thinks they arise from increased pressure in the bowel due to constipation or to an increased formation of intestinal gas. Wilson sums up his study as follows: "It may be stated briefly that diverticula of the lower bowel, while frequently following the course of the vessels, probably owe their origin more to congenital weakness of the circumferential musculature than to any other factor."

The clinical observation of acquired diverticulitis of the large bowel may be summed up as follows: All patients have certain features in common; most of them are over forty-five years of age; they are generally obese; males are affected more frequently than females; and excepting for this illness, the patients are otherwise in good health. The onset of symptoms is sudden, and characteristic of a localized peritonitis. The pain is acute and generally located in the lower left quadrant, comes in paroxysms and is associated with constipation. A tumor mass develops rapidly and usually is located to the left of the midline in the middle or lower quadrant of the abdomen.

The diverticulum becomes filled with stagnant feces and bacteria, and an inflammatory process is set up; this goes on to a peridiverticulitis and the formation of adhesions between the inflammatory mass and the bladder. The inflammatory process proceeds on to suppuration, and in some cases, a fistulous communication forms between the bowel and the bladder.

Tuberculosis is the second most frequent cause of entero-vesical fistula of inflammatory origin. In Sutton's series of thirty-four

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cases, there were six in which tuberculosis was the etiologic factor; there were two cases of tuberculous salpingitis, one case of tuberculosis of the left ovary and tube; one case of tuberculous peritonitis; one case of tuberculous and suppurative appendicitis; and one case of tuberculous postoperative fecal fistula. The other abdominal organs which were most frequently the site of a primary tuberculous lesion were the ileum, seminal vesicles, prostate and bladder.

Acute suppurative appendicitis with perforation is a rather common cause of fistula. The inflamed appendix becomes adherent to the bladder well, with a resultant inflammatory process in the bladder wall, which goes on to suppuration and the formation of a fistula between the appendix and the bladder. There are also cases in which an appendiceal abscess has drained through the bladder. Among other inflammatory lesions causing entero-vesical fistula are typhoid fever, syphilis, actinomycosis and infection in bladder diverticula.

In the cases due to tumor, carcinoma is most often responsible for fistula formation. The most frequent site of the primary lesion is the rectum, next the sigmoid, then the uterus and the bladder. In our series there was one case of carcinoma of the sigmoid, two of carcinoma of the bladder and two of carcinoma of the cervix. As a rule these cases are all far advanced when seen, and radical surgery is not indicated.

TABLE II
*342 Cases**

LOCATION OF FISTULA

Location	Number	Per Cent
Rectum and bladder	168	49.1
Sigmoid and bladder	81	23.6
Small intestine and bladder	16	4.6
Cecum and bladder	10	2.9
Ileum and bladder	16	4.6
Appendix and bladder	12	3.5
Colon and bladder	39	11.4

*Table based on cases collected from the literature.

The most common location of the opening in the intestinal canal is the rectum, and the sigmoid is next. Most of the thirty-nine cases listed under colon and bladder were probably in the sigmoid, but more definite information was not available. The location of the opening in the bladder is most frequently in the region of the trigone. In cases of diverticulitis of the sigmoid, the opening is to the left, this being due to the close proximity of the left bladder wall and the sigmoid. There are many cases reported in which the opening into the bladder was located on the posterior

wall, and a few on the summit of the bladder. The fistulous tract may be a direct communication between the bowel and the bladder, or a long and tortuous sinus. Carcinoma and tuberculosis generally give rise to the former, while the latter usually result from abscesses between the bowel and bladder, and an opening into these two structures at different levels.

The group of cases of congenital entero-vesical fistulae forms a small, but interesting series. Cripps reported thirteen cases in 1884. He found that they all occurred in the male, and that the anus was completely absent in the majority of cases. In six cases the fistula was between the prostate and the rectum; in three, it was between the rectum and the bladder; and in one, the bowel terminated at the sigmoid flexure, which communicated with the upper part of the bladder. He did not mention the location in the remaining three cases. Ten of the patients in this series died. I have been able to find only two cases of congenital fistula since that time, and with the addition of one of our own, the total is seventeen. One of these cases reported by Farr and Brunkow in 1925 had complete absence of the anus and the rectum emptied into the bladder. An anus was made and the rectum drawn down and opened. However, this did not relieve the abdominal distension, and a colostomy was done. The child died, and a postmortem examination showed the recto-vesical fistula. The other case was reported by J. D. Eschemindia (cited by Lower). In our case the anus was entirely absent and there was a fistula between the bladder and bowel at the recto-sigmoid junction. A colostomy was done the second day after birth. On the third day, feces and gas were passed per urethra. A few days later, the abdomen was opened and the fistula was resected. Later on an artificial anus was made and the bowel pulled down to the anal opening and sutured there. The child made a satisfactory convalescence, and is now eight years of age, has no urinary symptoms, and has good control of the bowels, except when the stools are watery.

Symptoms

The passage of gas and feces per urethra or the presence of urine in the rectum is pathognomonic of entero-vesical fistula. In eight of our cases there was a history of passing gas and feces per urethra. In one case there was no such history, but fecal matter was found in the bladder at cystoscopic examination. Prior to the establishment of a communication between the bladder and the gastro-intestinal tract, the symptoms depend upon the nature and severity of the disease, and the structure involved. Long standing complaints referable to the gastro-intestinal tract, such as constipation, transi-

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tory attacks of abdominal pain, and areas of localized tenderness over the abdomen will point to the intestinal tract as the probable origin of the fistula. Diverticulitis of the sigmoid usually is accompanied by pain and colic, most frequently in the lower left quadrant of the abdomen. There frequently is gaseous distension. Judd says that there is blood in the stool in 18 per cent of cases of diverticulitis. Pus and mucus in the stool is not uncommon in diverticulitis. If the inflamed diverticulum is close to the bladder, there will be frequency of urination, urgency and burning. Urinary symptoms are almost always present in some degree before the fistula is formed. Long standing bladder affections, especially where there is ulceration of the bladder wall, indicate that this organ gave rise to the fistula.

The symptomatology of entero-vesical fistula is quite uniform in all cases. The majority of patients show pneumaturia as the most constant and annoying single symptom. It is accompanied by an odor and may be heard some distance from the patient. Pneumaturia, according to Parham and Hume, may occur after, (1) instrumental vesical manipulation, such as lithopaxy, (2) in certain neuropathic conditions, and (3) in glycosuric conditions, the decomposing urine containing sugar. These conditions should, however, not be difficult to exclude in the presence of such symptoms as passing of feces and gas per urethra and the passage of urine by rectum.

Feces, however, are not always present in the urine. Frequently the communicating lumen is so small as to permit only the passage of gas. The symptoms of urine in the rectum are those of proctitis and are seldom of much consequence. Chavannaz says that urine is found in the rectum only in one-third of the cases. There was only one case in our series in which there was a definite history of having passed urine by rectum.

Renal infection is not uncommon in cases of entero-vesical-fistula. It is characterized by fever, chills and pain over the lumbar region. There were four patients in our series who had such symptoms. Pascal found kidney infection in eighteen of his cases and in fourteen it was bilateral. Sutton found definite kidney infection in only one of his thirty-four cases and says that it is not a common occurrence.

DIAGNOSIS

The diagnosis of vesico-intestinal fistulae as a rule should not be difficult. More important is the decision as to the part of the gastrointestinal tract involved in the fistula. The diagnosis usually can be made or suspected from the history, the cardinal symptoms being: (1) the passage of gas by urethra; (2) the passage of feces

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by urethra; and (3) the passage of urine by rectum. Chute stated that if the bowel contents found in the urine are dark, and contain solid food particles, it may be assumed that the connection probably is into the small intestine.

Cystoscopic examination reveals the opening in the bladder in the majority of cases. The bladder shows more or less diffuse inflammatory reaction, depending upon the size of the opening and the amount of feces coming through. It is not possible to demonstrate a fistula in all cases. In Case I the fistula was found only at necropsy. In Case VII fecal material and gas bubbles were seen coming through an opening in the bladder during cystoscopy. In two of our cases cystoscopic examination showed an opening in the bladder wall and on distending the bladder with saline, the solution passed through to the rectum, and the patient expelled it. In Case IV an opening was seen in the bladder and argyrol was put into the bladder and was recovered in the stools. In Case VIII a dark opening was seen on the vault of the bladder, but it was impossible to demonstrate a fistula by probing or overdistending the bladder. A cystogram sometimes shows the fistula.

The location of the site of the fistula in the bowel is determined by proctoscopic examination, barium, enema, and after filling of the bladder with a colored solution, watching its exit in the rectum. The location of the opening in the rectum by inspection is more difficult than is the opening in the bladder, because the folds of mucous membrane may obscure the rectal opening. By injecting some colored fluid into the bladder with the proctoscope in the rectum, it is frequently possible to observe its point of exit in the rectum. The location of the opening in the rectum can be demonstrated frequently by means of a barium enema, the barium passing through the fistulous tract into the bladder. A study of the lower bowel by the barium enema is of great value, also, in determining the type of lesion. In most cases of diverticulitis of the lower bowel, a characteristic filling is seen. Associated with this filling is a marked spasm of the bowel which greatly exaggerates the haustra and gives the bowel the appearance of a partially closed accordian. A filling defect in the rectum or sigmoid is more characteristic of carcinoma. In the differential diagnosis between carcinoma and diverticulitis must be considered the duration of the disease, and the general condition of the patient. Diverticulitis is characterized by the intermittency of its symptoms, the patient is in relatively good health and there has been no cachexia or progressive loss of weight, and fever and leucocytosis are quite common. The palpation of a sizable tumor mass in the sigmoid points more to diverticulitis than to carcinoma, where the lesion is circular and not easily

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palpable until late in the disease. In spite of all the diagnostic methods at our disposal, there are certain cases in which the diagnosis can only be determined by exploratory laparotomy.

PROGNOSIS

The prognosis depends upon the nature of the primary lesion producing the fistula. It is most unfavorable in the cases of malignancy. Many authorities contend that cases where tuberculosis is the primary lesion have a poor prognosis. However, Sutton reported good results in six cases of tuberculous origin. Another factor that influences the prognosis is the extent of the infection in the peritoneal cavity and in the genito-urinary system. Fistulae of inflammatory origin heal spontaneously at times. Case II of our series represents this group. In instances where the fistula is due to trauma or an inflammatory condition the prognosis is far more favorable. In the group of congenital cases, the outlook is poor. Of thirteen cases reported by Cripps, ten died, most of them at operation. The patient reported by Farr and Brunkow died a few days after operation. The patient in this series made a very satisfactory recovery.

In five of our cases the primary lesion was carcinoma; in three, the disease was too far advanced for radical surgery; and all these patients refused colostomy. In one, an exploratory laparotomy was performed and the disease was found to be so widespread that nothing could be done. In one case of carcinoma of the sigmoid with marked involvement of the bladder, cystectomy, transplantation of the ureters into the large bowels and resection of the sigmoid were done. This patient is still living six months after operation, but has signs of local recurrence. Of the first three cases, one lived nineteen months; one seven and a half months; and it has been impossible to trace the other. The patient on whom the exploratory laparotomy was done died ten months later. The remaining seven patients whose lesions were due to inflammation or trauma all are living, and the fistula has closed in all cases except one, where operation was refused. Though this patient is free from symptoms, cystoscopic examination still shows a small opening in the bladder wall. There was no operative mortality in the Cleveland Clinic series. One patient still has a colostomy which he has been advised to have closed.

TREATMENT

The treatment is essentially surgical, and may be considered as, (1) palliative, and (2) curative. The type of operation depends

primarily upon the nature of the pathologic process causing the fistula.

Under palliative treatment should be listed the removal of bladder stones, dilatation of urethral or rectal strictures to relieve obstruction, colostomy and suprapubic cystotomy. Colostomy is recommended to those patients who have advanced carcinoma of the bladder or rectum accompanied by marked bladder symptoms. Suprapubic cystotomy is done with the idea of allowing free drainage for the fecal contents in the bladder and should be reserved for cases of extensive carcinoma of the bladder in which nothing else can be done.

In cases in which trauma is the primary cause, or in which there is an inflammatory process, such as diverticulitis, appendiceal abscess, or salpingitis, radical curative surgery should be resorted to. This consists of abdominal section, excision of the fistula and repair of the opening in the bowel and bladder. At times it is necessary to resect a portion of the bowel, especially in cases with extensive diverticulitis. This was done in Case VIII of our series. The older writers suggested a preliminary colostomy as of advantage, especially in the inflammatory cases, as it diverted the flow of feces and gave the inflammatory process a chance to subside. Present-day surgeons do not use this procedure so frequently. The important point to be determined before performing a colostomy is the location of the fistulous opening into the intestinal tract, as the colostomy must be above the opening.

Some surgeons recommend perineal or vaginal approach in cases in which the communication is low down in the rectum. This operation seldom permits the closure of both openings of the fistula, and its success is based on separating the intestines from the bladder, and packing the wound, draining the bladder with an inlying catheter and preventing the bowels from moving until granulation tissue has formed in the opening.

The postoperative treatment of these patients is of the utmost importance. The patient should have inlying catheter drainage for at least ten days. The diet should consist of liquids for the first five to seven days, and then should contain very little residue for the following two weeks. In this manner there is little stress put on the closed areas. Some patients refuse operation, and in others, the disease is too far advanced to warrant operation. In these, certain measures must be carried out to make their condition more tolerable. The diet should be such as to contain the smallest possible residue and yet furnish the proper amount of nutrition. The bowels should be kept closed for a period of a few days and then evacuated by cathartics and enemas. The bladder should be irrigated daily

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CHART OF CASES

Case	Sex	Age	Etiology	Location	Symptoms	Duration of Fistula	Method of Diagnosis	Treatment and Operation	Results
I	M	53	Ca. bladder on right side just inside the internal sphincter.	Vesico-sigmoidal.	Urinary frequency, urgency, dysuria and hematuria. No history of gas or feces in urine and no diarrhoea.	Of the carcinoma, 9-12 mo. from history. Duration of fistula not stated.	Diagnosis of ca. by cystoscopic examination. Fistula was found at post-mortem examination.	Two courses of deep x-ray therapy.	Patient obtained some relief from urinary symptoms. Tumor decreased greatly in size. Patient died of metastasis 19 months after diagnosis was made. Postmortem showed ca. of bladder with involvement of sigmoid, a vesico-sigmoidal fistula and metastasis to the liver.
II	F	46	Fistula developed 2 weeks following pelvic laparotomy which was done elsewhere.	1 cm. above rt. ureteral orifice communicating with the rectum.	Watery discharge from bowel, urinary frequency and urgency, cloudy urine, fever, and chills. No history of passing gas or feces per urethra.	2½ weeks.	Cystoscopic examination showed an opening in the bladder and on overdistending the bladder with saline, solution passed into rectum and expelled.	Patient refused operation. The opening in the bladder was fulgurated several times. Diet with small residue prescribed, irrigation bladder and urinary antiseptics.	Only symptom patient complains of two years later is that stools are slightly watery at times. Cystoscopic examination shows very small opening still present, and on over-distending bladder with solution a small amount passes into the rectum.
III	F	60	Ca. primary in the cervix with widespread pelvic extension.	Rectum, bladder and vaginia.	Gas and feces per urethra, urine and feces in vaginia, loss of weight, marked urinary frequency and urgency.	3 months.	History of gas and feces per urethra. Cystoscopy revealed a large opening on left side of bladder through which there was a constant flow of fecal material; marked inflammation of the bladder. Solution introduced to distend bladder passed through the rectum and at once expelled. Proctoscopic examination showed opening in rectum.	Colostomy advised but patient refused this. Daily bladder irrigations, urinary antiseptics, non-residue diet and bowel regulation advised.	Patient died 7½ months after onset, evidently from pulmonary metastasis. No postmortem examination.
IV	M	70	Diverticulum of the bladder near the left ureteral orifice.	Between bladder and rectum.	Marked urinary frequency, urgency and burning. Passage of gas and feces per urethra, fever, chills, and chronic constipation.	About 2 months.	History of passage of gas and feces by urethra. Cystoscopy showed an opening just above the left ureteral orifice. A colored solution was introduced into bladder and recovered in rectum. Cystogram failed to show the fistula.	Abdominal section, excision of the diverticulum and the fistulous tract, closure of the openings from the bladder and rectum.	The fistula re-formed about ten days after operation. Patient treated conservatively with bladder irrigation, bowel regulation, etc., and two years later is free from any urinary symptoms and the fistula apparently has closed.
V	M	61	Ca. probably primary in the bladder.	Anterior surface of dome of bladder and colon.	Marked urgency, frequency and burning on urination, passage of feces and gas per urethra, chronic constipation, loss of 40 pounds in weight.	2½ months.	History, cystocopic examination showed opening in dome of bladder, unable to demonstrate fistula by cystogram or barium enema. Proctoscopic examination of no aid in the diagnosis.	Exploratory laparotomy. Condition was found to be inoperable. Colostomy advised, but patient refused.	Patient did not return after discharge from hospital. Died at home 10 months after operation. No postmortem examination.

pounds in weight.

CHART OF CASES — *Continued*

Case	Sex	Age	Etiology	Location	Symptoms	Duration of Fistula	Method of Diagnosis	Treatment and Operation	Results
VI	M	26	Patient swallowed straight pin when child. At age of 16 stone removed from bladder with the pin as its nucleus. Patient passed small stones on several occasions.	Appendix and dome of bladder.	Urinary frequency and urgency for 10 years. Urine always cloudy and foul smelling, material resembling feces passed per urethra for 2 years before admission to hospital.	About 2 years.	History; cystoscopic examination showed an opening in dome of bladder on right side. Unable to demonstrate fistula by cystogram or barium enema.	Abdominal section done and the tip of appendix was found to be adherent to the right side of the dome of bladder. The appendix was removed along with a small area of bladder wall. Examination of specimen revealed a fistula between the appendix and the bladder.	Patient completely cured; seen 20 months after operation and has had no recurrence of urinary symptoms.
VII	M	51	Abscess in diverticulum of the rectum which ruptured through into the bladder.	Posterior wall of bladder and anterior wall of rectum.	Onset with acute lower abdominal pain radiating to penis associated with fever, chills, urinary frequency and urgency and passage of foul smelling urine and gas per urethra.	1 month.	History of passage of gas and feces per urethra, cystoscopic examination showed an opening on posterior wall of bladder through which fecal material and gas bubbles were seen to pass. Examination of urine showed undigested food particles.	Abdominal section, an abscess containing foul smelling pus and communicating with the bladder and rectum was found. The abscess was drained and the openings in bladder and rectum were closed.	Uneventful convalescence; left hospital twenty-four days after operation with fistula closed. Patient seen 6 months postoperatively, and has had no recurrence of urinary symptoms.
VIII	M	50	Diverticulitis of the sigmoid.	Posterior surface of bladder and sigmoid.	Recurring attacks of colicky pain in lower abdomen, associated with constipation, urinary frequency, urgency, burning, cloudy and foul smelling urine. Patient not aware of having passed gas or feces per urethra, however, fecal material found in bladder at time of cystoscopic examination.	2 months.	Cystoscopic examination showed a dark opening on vault of bladder. Unable to demonstrate fistula by cystogram. Barium enema showed almost complete obstruction in mid-sigmoid but did not show the fistula.	Abdominal section; the sigmoid showed multiple diverticula, and at one point the sigmoid was adherent to bladder. Sigmoid was dissected from the bladder and it was found that there was a fistulous communication between opening in the bladder and bowel. The opening in the bladder was closed and the sigmoid reected and an end to end anastomosis was done. A cecostomy was done at the same time and the patient given a transfusion. Colostomy done 5 weeks postoperatively.	Patient developed a fecal and urinary fistula at the operation site eight days postoperatively and 16 days postoperatively developed an enterovesical fistula. Colostomy was performed 5 weeks later. The enterovesical fistula closed spontaneously 13 weeks after operation. General condition fine 7 months postoperatively, no urinary symptoms, still has a colostomy which he has been advised to have closed.
IX	F	68	Ca. probably primary in the cervix.	Between rectum, bladder and vagina.	Marked urinary frequency and urgency, passage of gas and feces per urethra and vagina, blood and mucus in stools, loss of weight and quite marked emaciation.	2 weeks.	History, pelvic examination showed a recto-vaginal fistula. Cystoscopic examination revealed an opening in the posterior wall of the bladder and on overdistending the bladder the solution escaped through the vagina and rectum.	Case was too far advanced for radical surgery. Colostomy advised but the patient refused. Put on bladder irrigation, regulation of diet and urinary antiseptics.	Unable to trace patient.

Case	Sex	Age	Etiology	Location	Symptoms	Duration of Fistula	Method of Diagnosis	Treatment and Operation	Results
X	M	42	Ca. sigmoid.	Between the sigmoid and bladder.	Marked frequency and urgency and hematuria, passage of gas and feces per urethra and loss of 15 pounds in weight.	5 months.	History of gas and feces per urethra. Cystoscopic examination showed fistulous opening between bowel and bladder with colored fluid and recovering it in the rectum.	Abdominal section; tumor mass found involving almost the entire bladder and four inches of sigmoid. Cystectomy was done, ureters transplanted into the sigmoid and the part of the sigmoid involved in the tumor mass was resected, and proximal end of the sigmoid used for a colostomy and the lower end was closed.	The ureter sloughed out of the sigmoid; patient developed an abdominal urinary fistula, left the hospital in 7 weeks in fair condition. Six months following operation still has the urinary fistula, colostomy working well. Patient has evidence of local recurrence of the malignancy.
XI	F	2 days	Congenital.	Recto-sigmoid junction and bladder.	Passage of gas and feces per urethra, starting the third day after birth.		History, passing gas and feces per urethra.	Child was born with imperforate anus. Colostomy done on second day after birth. On 7th day after the abdomen opened and fistula found between bladder and sigmoid. This was resected and the openings in the bladder and bowel closed. Several days later an artificial anus was made and the rectum was brought down and sutured to the opening. Colostomy was closed 5 weeks after operation.	Convalescence was uneventful. Fistula remained closed. Child now 8 years old and is completely free from any bladder symptoms. Only complaint is that at times the stools are watery and this causes fecal incontinence. Has good sphincter control otherwise.

and some soothing oily solution left in for the relief of the vesical irritation. Opiates should be used as indicated.

Conclusions

1. Entero-vesical fistulae are due more often to inflammatory or infectious processes than to carcinoma or trauma; diverticulitis is the most frequent predisposing lesion.

2. The most common site of the fistula is between the rectum and bladder, and next, between the sigmoid and bladder.

3. The cardinal symptoms of entero-vesical fistulae are (1) the passage of gas by urethra; (2) passage of feces by urethra; (3) passage of urine by rectum. Bladder symptoms of more or less severity are generally present, depending upon the size of the opening in the bladder and the amount of fecal material passing through. Proctitis is the most annoying bowel symptom, but is relatively uncommon.

4. Ascending kidney infection is not common.

5. Diagnosis depends upon the use of the cystoscope, the proctoscope, a study of the colon by barium enema, cystogram and the use in the bladder of a colored standard solution such as methylene blue to detect the opening in the rectum. Even with all these devices it is not always possible to demonstrate the presence of such a fistula before operation.

6. The prognosis depends upon the type of lesion causing the fistula. It is most favorable in those cases due to trauma and inflammation. Those due to carcinoma are generally far advanced when seen. In congenital cases, the prognosis is poor, because of the operative mortality. Some cases of inflammatory origin heal spontaneously.

7. Treatment is essentially surgical.

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DISEASES OF THE LARGE INTESTINE

C. C. McClure

Diseases and abnormalities of the large intestine are far too numerous to be described in one paper; I shall discuss, therefore, only the more common conditions that may be encountered in the routine examination of the gastro-intestinal tract.

The normal contour and position of the colon, as well as many of the abnormal positions that it may assume, are familiar to all physicians. It may not be so well known, however, that a transverse colon that crosses the upper part of the abdomen is more or less rare. In the majority of cases, one finds that the colon falls well below the umbilicus, and it is not unusual to find a transverse colon with its midpoint below the urinary bladder. In many cases the rotation of the colon is incomplete; frequently the embryonic stage is not fully resolved. The normal sigmoid flexure is generally from 16 to 17 inches long (40.6 to 43.1 cm.), but this length may vary, a redundant sigmoid sometimes being several feet in length. Doubtless some cases of obstipation are due entirely to this redundancy. The dilated colon, also, is often a source of difficulty. At the present time, extensive work is being done in an effort to prove that, in some cases at least, colonic stasis is directly responsible for arthritis, stasis being apt to occur, of course, when the colon is dilated, spastic or redundant. The intestinal activity is accelerated in the presence of hyperthyroidism, and diarrhea may be expected to occur; conversely, hyperthyroidism is held responsible for hypomotility of the intestines, with its accompanying symptoms of constipation and toxemia.

SPASTIC COLITIS

The etiology of spastic colitis has not been ascertained, although many theories have been advanced to account for the syndrome designated by this name; some writers even argue that it is not a definite condition, and many competent clinicians ignore its existence completely. It is my belief that spasticity of the colon is a real entity and one that can be definitely demonstrated. In the majority of cases, the condition does not become serious, although at times it causes alarming symptoms which may be readily misinterpreted. This misinterpretation occurred, in fact, in two cases that recently came under my observation.

In one of these cases the roentgenogram showed a constant filling defect in the sigmoid flexure. At operation, the only finding was spasticity in the area of the roentgenographic deformity. In the other case the same principle was illustrated, although the spastic area was not in the colon. All the cardinal symptoms of complete intestinal obstruction were present in the latter case, and

FIG. 1   FIG. 2

Fig. 1.— Roentgenogram illustrating a case of stone in the appendix of a child. This was a retrocecal appendix that had ruptured. The arrow points to the stone.

Fig. 2.— Megacolon in a child. Note that the colon almost entirely fills the abdomen.

consequently an operation was performed. The patient died on the operating table, and at autopsy a spastic area in the jejunum was disclosed. Had a test been made with atropine or some other antispasmodic, doubtless an operation would not have been performed and the patient would still be alive.

Spastic colitis is a functional condition that may give rise to numerous symptoms, the most common of which are constipation flatulence, abdominal malaise and pain (either localized or general). If the spasticity persists, it may lead to an inflammatory change with its accompanying symptoms. Since constipation is the most constant symptom, it is surprising to learn that often there is marked colonic hypermotility, the head of the barium meal reaching the rectum in a few hours. This is not difficult to understand, however, in view of the mechanism that causes spastic colitis. According to Gauss,[1] several theories have been advanced to explain hypertonicity. Among these theories are those of an unstable
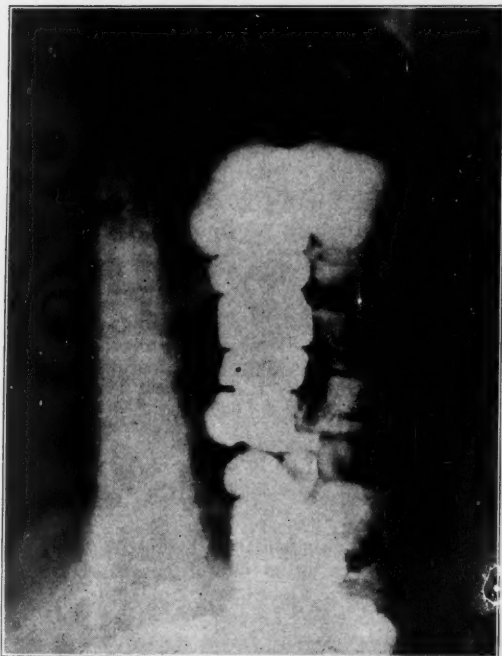
Fig. 3.— Roentgenogram showing a portion of the colon herniated high into the left pulmonic field.

nervous system, a submerged fear complex acquired in early life and an inherited spasmophilic tendency. "The direct etiologic factor is an open problem today. Nevertheless, it has been observed that usually the patient with a spastic colon is a neurotic individual given to introspection, and that the hypertonicity of the colon is a local manifestation of a general spasmophilic tendency." Spasticity, no doubt, is the underlying cause, this being due to a variable degree of reflex contraction of the smooth muscle fibers.

ULCERATIVE COLITIS

It is probable that ulcerative colitis is caused by an infection that has been superimposed on tissues the resistance of which has been lowered as the result of a predisposing condition, such as long-standing catarrhal inflammation of the bowel or severe spasticity of the colon. The ulcerations vary greatly in size, some being only as large as a pinhead while others completely surround the lumen of the colon. Some ulcerations may be very superficial, becoming

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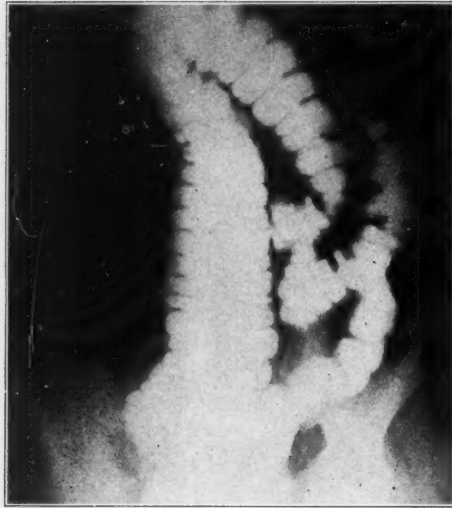
Fig. 4.— Roentgenogram showing an abnormal position of the proximal colon. Scarcely any of the colon is seen to the right of the midline. The cecum and appendix are low in the pelvis.
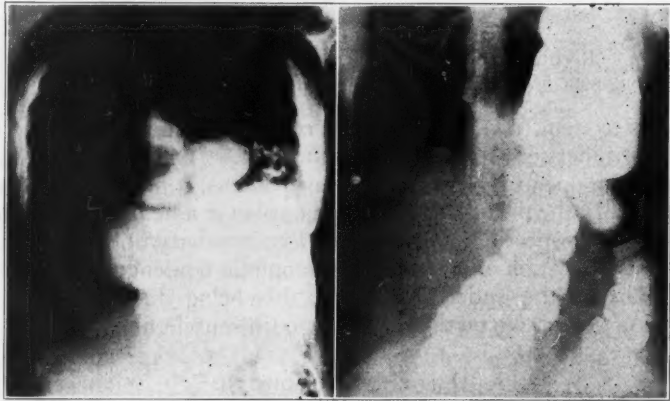

Fig. 5.— Roentgenograms showing hernia of the diaphragm on the left.

completely healed in a few days, while others may extend to the muscular coat or may even penetrate the wall of the colon and involve the peritoneum.

The disease is apt to be sudden in its onset, with lancinating pains over the course of the colon, accompanied by griping and

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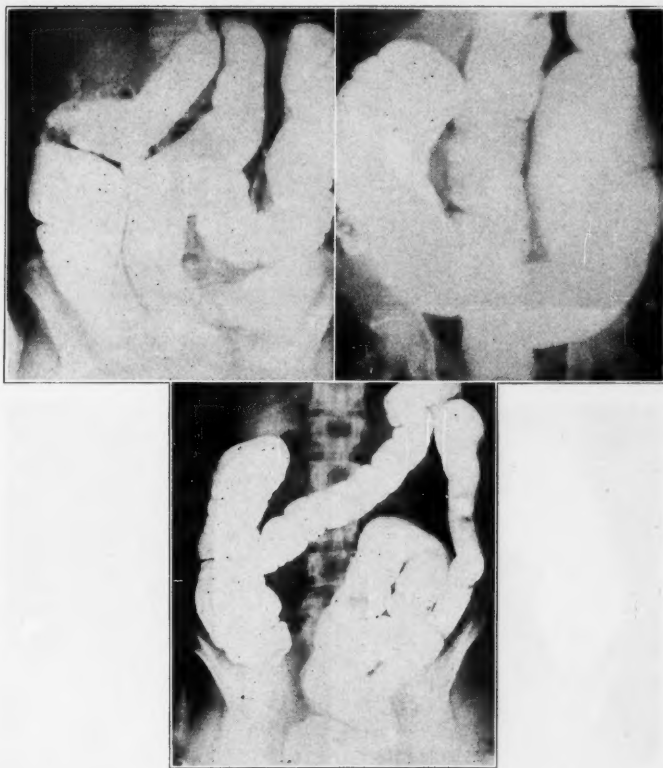
Fig. 6.— Roentgenograms showing varying degrees of redundant sigmoid.

frequent bowel movements. There are severe constitutional disturbances, and in those cases in which the disease is progressive, despite treatment, the resulting mental condition parallels the effect of the toxemia on the nervous system. These attacks occur in cycles, and between them the patient has complete comfort. After a few attacks, mucus, pus and blood are passed, and in severe cases the condition of the patient is distressing.

Ulcerative colitis may be confused with dysentery, typhoid fever or a malignant condition. It presents many of the characteristics of the later stages of bacillary dysentery, but is not so fulminating in its onset and does not produce profound toxemia, and the fever seldom is as high as in the former condition. The final differentiation, however, depends on the results of stool cultures and agglutination tests. Amebic dysentery is more gradual in its onset;

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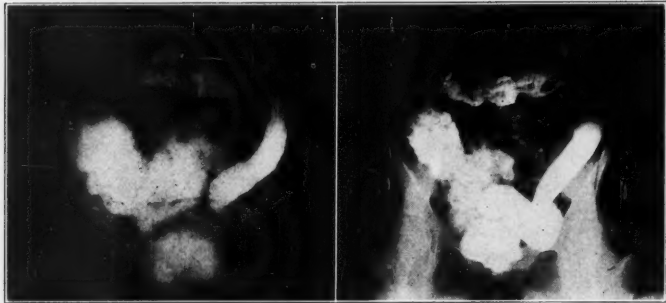
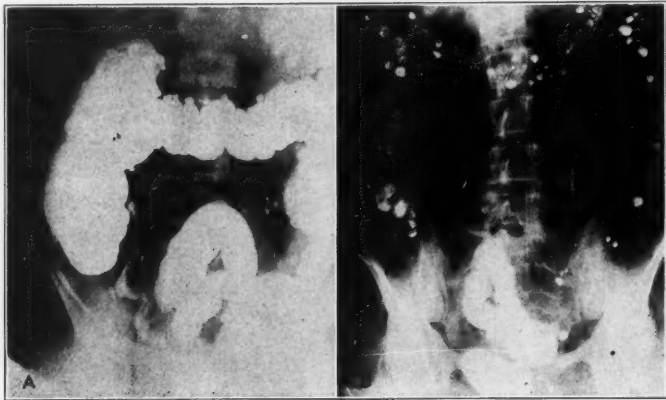Fig. 7.— Two cases of chronic ulcerative colitis. Note the loss of tone in the colon.

Fig. 8.—(A) A case of diverticulosis. Note the diverticula along the entire course of the colon. (B) Roentgenogram of a typical colon twenty-four hours after the administration of barium, showing many diverticula.

it presents stools containing amebae and gray, blood-stained or yellow mucus, and the condition of the patient is improved after three or four days of treatment with emetine hydrochloride. In this country, chronic bacillary dysentery is less common than is chronic ulcerative colitis, and its diagnosis is made by agglutination tests. Examination with the sigmoidoscope may reveal tumors or ulcers in the rectum and permit the obtaining from them of mucus, a slough or a scraping for examination or culture. A roentgenogram may be helpful in the recognition of colitis by revealing the presence of spasm or areas of ulceration.

Typhoid fever may be differentiated from ulcerative colitis by a history of exposure to a source of infection, followed in two or three
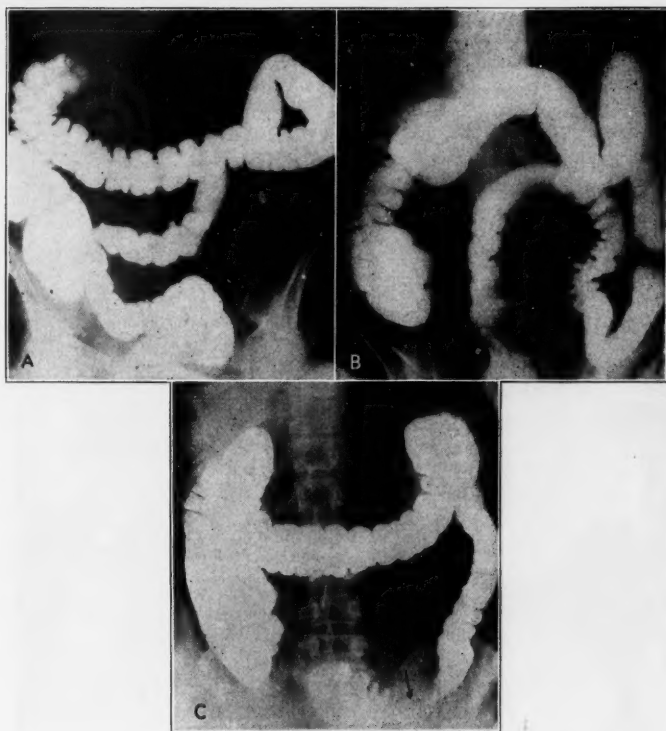
Fig. 9.— (A) Roentgenogram of sigmoid extending to right lower quadrant. Note several small diverticula in the sigmoid. (B) Diverticulosis of the sigmoid. Note the long loop of sigmoid with evidence of pressure from an extrinsic mass. (C) Roentgenogram showing almost complete obstruction in the sigmoid due to a large inflammatory mass in the area designated by the arrow. The presence of several small diverticula proximal to the lesion is evidence in favor of a nonmalignant tumor.

weeks by an insidious onset, and at the end of another week by the development of rose spots and enlargement of the spleen. The temperature curve in typhoid fever usually is characteristic, and there are progressive leukopenia and lymphocytosis. Blood cultures may give positive results as early as the second day, and the Widal reaction is positive after the tenth day.

Cancer develops much more slowly than ulcerative colitis, and pain and griping are rarely seen early in malignant disease. Constipation is one of the earliest symptoms of carcinoma, as is the case in colitis, but in a case of carcinoma the patient is comfortable

Fig. 10.— (A) Roentgenogram showing the cecum lying high in the right upper quadrant. It is in such cases as this that a diagnosis of appendicitis is difficult. (B) A similar case. The arrow points to the tip of the appendix lying high under the liver. (C) Roentgenogram showing the cecum lying in the midline. (D) Roentgenogram showing the cecum lying far to the left. Should appendicitis develop in this case, it would be difficult to diagnose. Symptoms would be referred to the lower left quadrant.

after the bowels have moved, except in the late stages of the disease, while in colitis a bowel movement fails to give relief.

PERICOLITIS

The manifestations of pericolitis vary with the duration of the condition, the type and virulence of the infecting organism and the length of intestine involved. The chief symptoms are constipation, alternating with occasional diarrhea, constitutional disorders resulting from absorption, localized abdominal soreness or pain
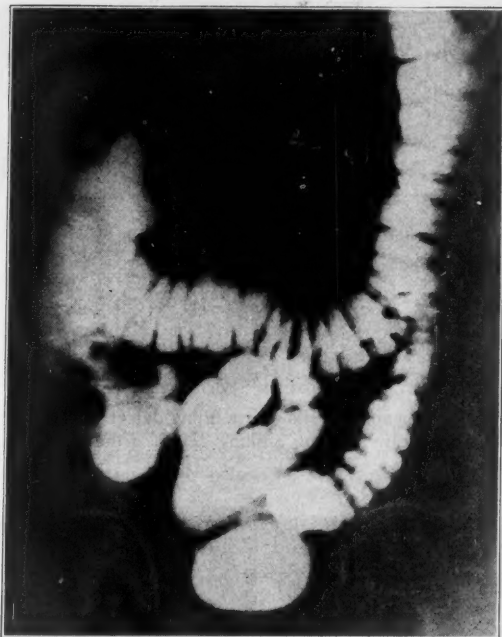
Fig. 11.— Roentgenogram showing a large filling defect in the first portion of the ascending colon due to carcinoma.

on pressure, a palpable abdominal mass, which may readily be mistaken for a tumor, and mucus or blood in the stools. Mild and sometimes alarming symptoms of intestinal obstruction may be present, depending on the degree of narrowing of the lumen of that portion of the colon involved. In cases in which the temperature is high, an abscess may be suspected.

In obscure cases it is necessary to differentiate between this condition and appendicitis, diverticulitis and cholecystitis. Fluoroscopic examination and roentgenograms following a barium sulphate enema will often aid in making the differential diagnosis, although in diverticulitis the enema is not so important as the twenty-four hour barium examination, since barium sulphate when given by mouth is so much more certain to fill a diverticulum than when given by enema.

APPENDICITIS

I do not mean to imply that all cases of appendicitis can be diagnosed by roentgenograms, but many cases cannot be diagnosed pre-
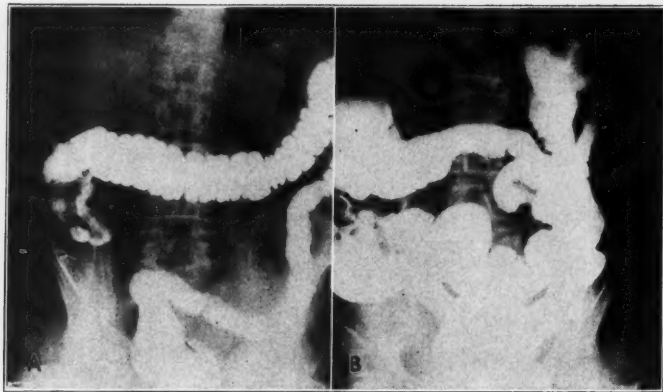
Fig. 12.— (A) Roentgenogram showing a filling defect in the cecum due to carcinoma. (B) Roentgenogram showing a filling defect in the ascending colon due to a large carcinoma.
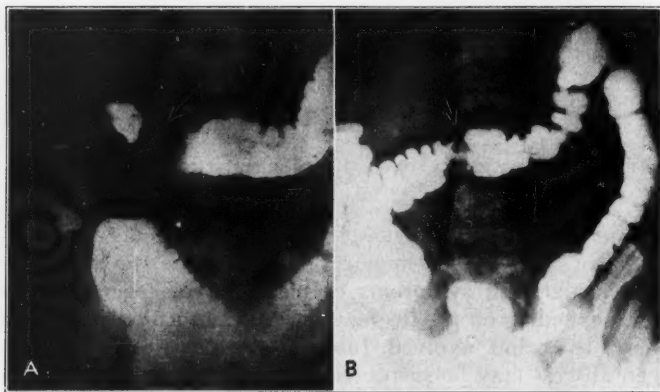

Fig. 13.— (A) The arrow points to a deformity in the transverse colon due to carcinoma. (B) A similar case, but less obstruction is present. However, note the beginning dilatation of the colon proximal to the obstructing area.

operatively by any other method. Acute appendicitis is not a problem for the roentgenologist, but one that should be handled promptly by the surgeon. The cases in which roentgenographic study is of value are those in which there is a history of vague abdominal uneasiness or distress, with a digestion that is not up to par. In many instances suspected cholecystitis can be ruled out by the roentgenographic demonstration of incomplete rotation of the colon which leaves the cecum and appendix in the region of the
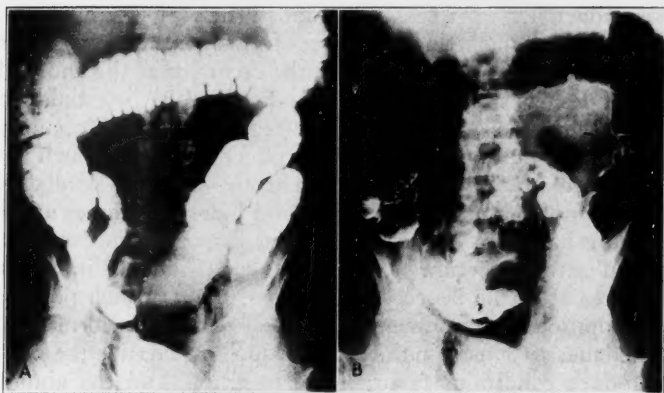
Fig. 14.— (A) A filling defect as seen fluoroscopically in the lower descending colon. The loop of the sigmoid obscures the deformed area. (B) The same case after air has been injected into the colon. The arrow points to a filling defect due to carcinoma.

gallbladder. Often also it is possible to demonstrate the presence of an elongated retrocecal appendix with the tip high up under the hepatic flexure, a finding that is of value in the differential diagnosis and of assistance to the surgeon in planning his incision. The presence of stones in the appendix also can be demonstrated roentgenographically, as well as adhesions that prevent the free movement characteristic of the normal appendix. In other types of appendiceal disease an irregular filling can be demonstrated that corresponds to definite localized tenderness. It is not often that the appendix is found in the classic McBurney position, but it can be localized accurately with x-rays, while pressure will determine the presence or absence of tenderness. Delayed emptying of the appendix (from twenty-four to seventy-two hours after the head of the colon has emptied) is thought by some authorities to be evidence of chronic appendicitis.

FOREIGN BODIES

The presence of foreign bodies can be demonstrated roentgenographically only when they are of opaque material. Serial roentgenograms and fluoroscopic examinations are essential in order to follow the progress of the foreign body through the intestinal tract and to make sure that it has not lodged at some vulnerable point.

TUBERCULOSIS

Tuberculosis of the colon and rectum may be either primary or secondary. In a review of 100 cases, Gant[2] found that the infection

was secondary in 75 per cent, and that in the majority of these the foci were located in the lungs, larynx or pharynx. Primary tuberculosis of the colon usually develops in the cecum or at the anus, while secondary lesions may be found anywhere in the intestinal tract, although they, too, are found most frequently in the cecum and rectum. Many factors contribute to produce this result, such as the greater speed of the intestinal content through the small bowel, which does not permit the bacilli to find lodgment there; attenuation of the bacilli by the gastric juices, their virulence not being recovered until the cecum or colon is reached; the alkaline reaction of the feces after the ileocecal region is attained, which provides a more propitious environment for the bacilli; the formation of hardened masses of feces in the cecum, which traumatize the mucosa and produce conditions favorable to infection, and the abundant lymphatic distribution in the ileocecal region, which favors the development of tuberculosis.

Several types of tuberculosis are found in the colon, the most common of which are the hyperplastic, ulcerative and miliary.

Hyperplastic tuberculosis occurs in both children and adults, most frequently in the third decade. It may be primary or it may be secondary to a focus higher up in the intestines or in some other organ. It produces a slow-growing tumor which at times is quiescent for two or three years before it attains sufficient size to occlude the lumen of the intestine and produce symptoms of obstruction. These tumors usually feel smooth when palpated, but examination of a gross section reveals a very irregular, hard and brittle type of tissue. Usually they are fixed, but they may be slightly movable. The rigidity of the terminal ileal segment is a characteristic roentgenographic observation.

In the ulcerative type of tuberculosis, the ulcers may be superficial or deep. Superficial ulceration may heal promptly, but deep ulceration progresses rapidly and is almost impossible to control. The mixed infection that must follow soon causes toxemia, imperfect digestion, constitutional manifestations, persistent diarrhea and extensive destruction of the mucosa and deeper bowel coverings. Hemorrhage, peritonitis, abscess, adhesions and other serious complications may be encountered, and if surgical intervention were instituted, a generalized miliary tuberculosis of all the abdominal viscera might be found.

The prognosis of intestinal miliary tuberculosis is unfavorable because it is secondary to a well established process elsewhere, and the patient is debilitated and unable to withstand the ravages of the fast-spreading tuberculous process.

Fig. 15.— Roentgenogram showing carcinoma of the sigmoid. This could not be seen with the patient lying flat. The film was exposed with the right side of the patient uppermost. The sigmoid is a frequent location for carcinoma. The coils of the lower sigmoid and rectum overshadow these growths.

DIVERTICULA

A diverticulum is a non-neoplastic outpouching of intestine, having a lumen that connects with the bowel or that formerly con-connected with it. Diverticula may be congenital (true) or acquired (false), the latter form appearing more often between the ages of 40 and 60 years, and about twice as frequently in men as in women. Diverticula may develop at any point along the course of the colon, but are found most commonly in the sigmoid flexure, the descending colon, the cecum and the transverse colon. The hepatic flexure also is frequently involved, and diverticulitis at this point is at times most difficult to differentiate.

Diverticula may be single or multiple, large or small, smooth or irregular. The sacs may be quiescent for many years and then suddenly become obstructed, resulting in acute inflammation. Symptoms may then become severe and lead to the belief that appendicitis, peritonitis, intestinal obstruction, a new growth, or an abscess is present. Definite proof that many diverticula never produce symptoms is presented by the frequent finding of such pouches during the course of routine gastro-intestinal examinations and at autopsy.

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Diverticulitis may be acute or chronic, more often the latter. Because of the size, form, consistency and macroscopic appearance of the tumor, a diverticulum often is mistaken for carcinoma. Doubtless many of the supposed carcinomas that have been reported cured by operation have in reality been merely inflammatory masses caused by diverticulitis. It may be that these diverticula are a predisposing cause of carcinoma, but to determine this definitely would require extensive research.

After the onset of inflammation in a severe case of diverticulitis, there will be localized tenderness, intense cramps and constipation with a sensation of blocking. When the lumen is almost occluded there are a marked formation of gas, severe pain, muscular rigidity, nausea and vomiting, an increased temperature and pulse rate and mucus, pus and blood in the stools. If the process progresses to the point of rupture, the usual symptoms of spreading peritonitis are present. If an abscess forms, there is continued localized pain and swelling until it has ruptured into the intestine or peritoneal cavity or has been drained.

Given a history of chronic left-sided inflammation, with periodic exacerbations and an absence of cachexia and loss of weight, a diagnosis of diverticulitis usually is justified. Proctoscopic examination may reveal a small opening from which pus is draining, and pus in the bowel is suggestive of diverticulitis.

If the patient's condition is extremely grave, it is not advisable to subject him to a roentgenographic examination. Cases have been diagnosed, however, in which the obstruction was almost complete, a barium sulphate enema showing the filling defect. It is often impossible to make the differentiation on the basis of the roentgen examination alone, but the small cavitation that is present in carcinoma is rarely seen in diverticulitis. The deformity, of course, is due to narrowing of the lumen of the colon, but in diverticulitis there is, as a rule, no break in the mucosa and the rugae can be seen in the deformity.

CARCINOMA

Unfortunately, early carcinoma of the colon is difficult to diagnose roentgenographically, as a filling defect does not develop until the late stages of the disease. It is impossible to see the early ulcerations, and a mass must be present that will displace a portion of the column of barium sulphate in the colon before a diagnosis can be made. After the growth has become large enough to produce partial obstruction, dilatation of the colon proximal to the lesion will be noticed. In many instances carcinoma of any portion of the

colon may be overlooked if redundancies cover up the lesion. A fluoroscopic examination should be made from all angles, therefore, in an effort to throw these redundant loops out of the field of vision and pick up some small filling defect on either the anterior or the posterior wall of the intestine. Patients suffering from early carcinoma of the colon, however, seldom present themselves for roentgenographic examination.

Fully developed cancer of the colon usually produces fairly typical symptoms: alternating constipation and diarrhea, distention of the colon, tenderness, localized abdominal pain, attacks of offensive discharge containing mucus, blood, pus and possibly tissue fragments, loss of weight, cachexia, visible peristalsis and a filling defect, with evidence of dilatation of the colon proximal to this defect. It is often difficult to pass any of the opaque medium through the area of partial obstruction when the barium meal is given by enema, though a small amount may pass the obstruction when the barium meal is given by mouth. Atropine and other antispasmodics offer little assistance in the passage of the enema through the deformed area. When cecal carcinoma is suspected, a delay in ileal emptying is a significant sign. A proctoscopic examination should always be made before a barium sulphate enema is administered, in order to detect any evidence of the disease that may be visible in the rectum or lower bowel. Barium sulphate should not be given before this examination is complete, as it coats the bowel and obscures any evidence of disease that may be present.

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THE TREATMENT OF MALIGNANT GROWTHS OF THE MALE URETHRA

A Clinical Report

William E. Lower, M.D.

That primary carcinoma of the male urethra is a comparatively rare condition is evidenced by the small number of cases reported in the literature. In 1922 Braasch and Scholl[2] published a complete review of the literature up to that date, and reported a case. Since that time additional cases have been reported by Kretschmer[8] in 1923, Culver and Forster[4] in the same year, Christen[5] in 1925, Neuwirt, Bedrna[9] and Peters[10] in 1928. In 1928, additional cases were also reported by Fukai,[6] and in 1929 by Flamm,[5] Bieberbach and Peters,[1] and also Huggins and Curtis,[7] bringing the total number reported in the literature up to 110 cases.

To this number I wish to add three cases which have come under my observation and in which operation has been performed. All three patients are living at the present time without any signs of recurrence, one for nine years, one for eight years, and one for three and one-half years after operation. In one case there was a history of injury to the perineum; in another a history of long standing inflammation of the urethra followed by stricture, and in the third there was also a history of chronic urethral inflammation. In two of the three cases a local resection of the urethra was performed with end-to-end anastomosis. In both of these cases stricture followed; in one case an internal urethrotomy was necessary and the patient still has a rather firm, tight stricture, although he is not greatly inconvenienced. In the other case the urethra is about normal in size with a tendency to narrowing after intervals of six months, if it is not dilated. In neither case, however, is there any evidence of metastasis. In the third case extensive metastases were present in the inguinal glands, and there was extensive urethral involvement. This patient had a double inguinal hernia, and was also a diabetic. A block dissection was done in this third case, in which the penis and urethra anterior to the growth were removed, together with the testes and inguinal glands; the proximal urethra was transplanted into the perineum, and the herniæ were closed. The patient made a good recovery and is free from any evidence of recurrence at the end of three and one-half years.

The pathological diagnoses in these cases were squamous cell carcinoma in the first case, papillary carcinoma in the second case, and adenocarcinoma in the third case. In this last case the growth probably started in some of the glands adjacent to the urethra, but for clinical purposes it may be classified as of the urethra.

It is difficult to make an early diagnosis in these cases. The symptoms are largely those of stricture with attendant abscess formation, and the real cause of the trouble may be overlooked until extension has taken place. If the condition can be recognized early, operation offers very good chance of permanent relief. Our experience has confirmed other reports that carcinomata of the male urethra do not metastasize early. Fistulæ are nearly always present. These tumors occur mainly in the membranous portion of the urethra.

From the history of the cases coming under our observation, traumatism and chronic irritation were the predisposing causes.

The success of the surgical treatment depends upon the stage of the disease at which it is instituted. If the cases can be treated early, while the condition is still localized, the results will be good, as attested by our experience in the three cases described here. In one case there was extensive involvement of the inguinal glands, but we hope the process was checked at this point. Although three and one-half years have elapsed, it is still too early to consider the cure complete. X-ray and radium following excision is to be recommended and may be of benefit. If the case is inoperable, certainly radiation should be employed.

Case Reports

Case 1. The patient was a laborer, fifty-eight years of age. There was nothing in the general history having any bearing on the condition which was present. He gave a history of some sort of injury to the perineum some years previously, which was followed by a rectal fistula. Two years before being admitted to the clinic he had had an acute retention which was caused, he said by a cyst of the urethra. No definite history of this condition could be obtained except that a perineal incision had been made for the relief of retention; this was followed by a fistula.

At the time I saw the patient an acute retention was again present, together with extensive perineal induration, infection, chills and fever. A suprapubic puncture was made for relief of the retention. After the acute symptoms had subsided, and much of the perineal edema had been reduced, an operation was undertaken

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for the relief of the stricture. At this time I was not sure that this condition was malignant, although it was unusually hard. The operation consisted in opening the bladder and passing a sound retrograde. At the tip of the sound in the perineum, the urethra was divided, the mass was dissected free and the distal end of the urethra was severed beyond the involved tissue. About 1.5 inches of urethra was resected. By passing a No. 18 catheter from the meatus, an end-to-end anastomosis was made. Convalescence was rather slow, but after a reasonable time the catheter was removed. A small perineal fistula remained, which, however, soon closed. Regular dilatation has been continued, this being necessary now only about twice a year. The patient is in good physical condition, and there is no evidence of recurrence after nine years.

The histological diagnosis in this case was squamous cell carcinoma.

Case 2. This man, forty years of age, gave a history of a gonococcus infection at the age of twenty-two. Eleven years before being admitted to the clinic he had had an acute retention which was relieved by perineal incision. This was followed by a stricture requiring frequent dilatation.

When I saw the patient in 1923 an acute retention was present and I was unable to pass any kind of instrument past the stricture. I relieved the retention by a suprapubic puncture. A very hard, indurated area was found in the perineum. Remembering my experience of a year previous with a similar condition, I made a diagnosis of probable malignancy. A resection was done as in the previous case, and a course of x-ray therapy was given following operation. Union at the point of anastomosis of the ends of the urethra was not very satisfactory and a very tight stricture resulted. An internal urethrotomy was performed two years later, and since then dilatation has been done at regular intervals. There is no evidence of recurrence after eight years.

The histological diagnosis in this case was papillary carcinoma.

Case 3. This man, sixty-one years of age, gave a history of a gonococcus infection at the age of twenty-five. He was admitted to the clinic on account of difficulty in urination. Extensive induration was present in the perineum extending along the entire urethra. The inguinal glands on both sides were involved; a biopsy of a gland showed malignancy. Nothing short of an extensive block dissection seemed worth while. The hazard of such a procedure was explained to the patient and his family; he requested that the operation be performed.

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The penis and the testes and inguinal glands on both sides were removed and the urethra was transplanted into the perineum. Bilateral herniæ were present which were easily corrected after the testes and inguinal glands had been removed. The patient was also diabetic, but is no longer handicapped by this condition. After three and one-half years he seems to be perfectly well and there is no evidence of recurrence.

SUMMARY

1. Practically all published reports of cases of malignancy of the male urethra stress the difficulty of an early diagnosis.

2. The condition is often associated with, and resembles the induration of an infection about a stricture.

3. The condition does not produce early metastasis.

4. Operation, even without resection of the inguinal glands, may produce good results.

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POSTOPERATIVE ROENTGEN THERAPY FOR CANCER OF THE BREAST. A REPORT OF 103 CONSECUTIVE CASES

U. V. Portmann, M.D.

Carcinoma of the breast has always been looked upon as primarily a surgical problem. Within recent years the analysis of the results which are obtained by surgical procedures, together with our thorough understanding of the clinical course of the disease, would seem to give rise to the question as to whether or not operation alone is the final and satisfactory treatment of this disease.

Surgical extirpation of any malignant process in any location, by any technic, will completely eradicate every neoplasm if it is so localized that it has not extended beyond the area which can be excised. Unfortunately such a favorable condition is seldom encountered and it is very uncommon to discover a case of cancer of the breast in which foci have not developed throughout the gland and extended into neighboring tissues, or in which the cancer has not metastasized to the adjacent lymph nodes or more distant areas. This fact is well demonstrated by examination of massive cross sections of the entire breast in which numerous nests of neoplastic cells are found scattered throughout and involving most of the structures in a majority of specimens. Also it is well known from the reports of competent pathologists that the axillary nodes are involved in 95 per cent of specimens which are examined. It is very questionable that malignant disease can be completely eliminated when the axilla is involved, even by the most skillfully performed operation, and it is probable that neoplastic cells remain after operation in a majority of instances. The axillary lymphatics drain directly into the supraclavicular nodes which are seldom removed because of the lack of clinical evidence of involvement. However, these supraclavicular nodes must be involved more frequently than is realized. The peristernal lymph nodes which are likewise inaccessible often are diseased.

The above facts indicate that in the majority of cases, cancer of the breast is a much more extensive process than is usually appreciated and therefore the most radical operation by any technic can seldom eliminate all of the neoplastic cells which may be present beyond the comparatively limited fields which are accessible to the surgeon. It is equally certain that operation is of little value

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to the patient as far as cure is concerned when neoplastic cells remain. That it is usually difficult to remove all neoplastic cells is exemplified by the well known fact that metastatic and local recurrences are more likely to develop in obese individuals following operation more rapidly than in the case of the less robust individual. There are some who think that this is due to some inherent lack of resistance in obese persons but it is much more likely that the surgeon does not extract sufficient pounds of flesh from a large enough area because of the subsequent difficulty in covering the widely denuded area, and therefore neoplastic cells remain in the fat interspaces and in the skin where they develop very quickly and without restraint.

In most of the statistical reports of the results of operation it is assumed that if a patient who has been operated upon for cancer of the breast has survived for from three to five years without evidence of the disease the operation has effected some degree of benefit. However, if we study the clinical course of this disease in a large group of cases, we will be impressed by the fact that some individuals harbor neoplastic cells or even well-developed malignant tissue for several years without detriment to their wellbeing, and also that with or without operation, neoplastic cells may remain dormant for a long time before manifesting activity. For example, I treated a woman for vertebral metastases of a few months duration, having developed from a fairly small proven cancer of the breast which undoubtedly, at least from clinical evidences, began 27 years previously. It is not unusual to observe locally recurrent cancer long after operation, the longest period in my experience being 22 years.

We must also remember that cancer of the breast per se does not destroy life, but becomes fatal only when it has destroyed the function of vital organs. The process is a comparatively localized one lasting for varying periods of time during which none of the affected structures are essential to life and may be more or less destroyed by cancer without affecting the health of the host. Therefore, we may not assume that the cancer which may involve these structures will immediately cause the death of the patient, nor that we have materially benefited or cured her by removing some of them by operation.

A review of a multitude of reports of statistical studies of the results which are obtained by operation for cancer of the breast shows that an average of approximately 40 per cent of patients are free from manifestations of the disease for a period of three years, and about 30 per cent for five years. Also a number of reports

show that the average natural duration of life of patients with cancer of the breast is approximately three years. If an average of only 40 per cent of cases that are operable survive for three years after operation which is the natural duration of life, we may very well question just how much is usually accomplished by radical operation for cancer of the breast, and there must be some doubt that surgery alone is an entirely satisfactory solution of the problem of the treatment.

The question, when is a cancer of the breast operable from the standpoint of curability, is very pertinent. Since 1897, when the radical operation was first advocated by Halstead, about 10 per cent more patients survive for five years after operation than was formerly the case. However, with this radical operation the surgeon has reached the ultimate limit of the amount of tissue which he is justified in removing by any technic and beyond which cancer frequently exists. Therefore, it must be apparent that some means must be devised whereby we may replace this radical surgery by a more or equally effective method, or that some beneficial procedure must be instituted to carry on as an adjunct because of the known limitations of operation.

It is about 30 years since roentgen rays and radium were first employed as therapeutic agents. It was soon found that some degree of benefit was derived when they were applied in the treatment of neoplastic diseases, even with the comparatively inefficient and limited technic which was then employed. It is only during the past 10 years that we have known enough about the biological and physical properties of these agents to take them out of empirical therapy and establish them upon a scientific basis. The radiation therapy of even fifteen years ago may be compared to that dark era in surgery of three thousand years before Christ when, as the papyrus of Ebers tells us, it was recognized that axillary involvement is associated with cancer of the breast, and attempts were made to treat the disease by cautery, a method not unlike some of those which are in vogue in this present age of scientific enlightenment.

It is interesting to note that there are some individuals who still deny the possibility that radiation therapy may be of value in the treatment of cancer of the breast but they will admit having observed benefit in some hopelessly advanced cases or after recurrences or metastases have developed. It would seem to be a logical deduction that if radiation is of benefit in some of these cases which are hopeless from a surgical standpoint, others with earlier or less extensive involvment might also be benefited by radia-

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tion. Usually this skepticism is due to ignorance of the clinical course of the disease, badly correlated statistical studies, lack of understanding of the methods of applying radiation and of its effects, or to the observation of only inefficiently applied treatment, and not infrequently to the fact that the cases which are referred for treatment are the least favorable. There are also some who are so poorly informed that they believe that radiation may stimulate a malignant process, in spite of numerous clinical and experimental reports and evidences to the contrary. The very fact that recurrences do appear after thorough postoperative roentgen therapy for cancer of the breast at once indicates that resistant neoplastic cells have remained after operation for which the surgeon must assume the entire responsibility, because radiation has not the magic power to spontaneously germinate seeds of cancer in a field where none have previously existed.

Radiologists and others can not reasonably expect favorable results in every instance. Unfortunately, there are many patients who might be benefited by radiation who are still denied even this possibility. However, I know of no basis on which we can determine which cases will be benefited without trial in each case.

Radiation therapy, as it is understood today, consists of the application of radium and roentgen rays in accurately measured and predetermined dosage in the proper location according to the individual indications. There can be no routine inelastic procedure. It is not only desirable, but essential, that each patient in whom a malignant disease is present should have the benefit of consultation and cooperation between the surgeon and the radiologist, each of whom is familiar with the technical details and the results of the other's method of treatment, as well as the limitations of his own. Thus, it must be decided whether the patient should be operated upon, whether preoperative or postoperative roentgen therapy, or both, should be utilized, or if radium should be applied, and when and how, or whether radium should be combined with roentgen ray.

This discussion is limited to postoperative roentgen therapy and therefore other therapeutic procedures are not considered. A report is presented of a series of 103 consecutive cases of patients who were operated upon and received roentgen therapy immediately postoperatively, during the years from 1922 to 1925, inclusive. I have not included those cases which were referred during this period for roentgen treatment of recurrences or metastases or those which were considered to be too far advanced to be operated upon, nor those treated by other procedures. Each case has had microscopic confirmation of the diagnosis although in a few instances the type of

TABLE I

Summary of 103 Consecutive Cases of Breast Cancer Treated by Postoperative Roentgen Therapy

Group		No. cases	Skin invol.	Tumor fixed	Clin. axil. nodes	Clin. supracl. nodes	Recurrences	Metastases	No trace	Died		Alive 5 Years		
										Not ca.	Of ca.	With ca.	No ca.	With or Without ca.
I	No.	3 Bilat. 2	3	0	2	0	0	2 2 Bilat?	0	1	0	2 Bilat. 0/2	6	7
	%		33.3	0	22.2	0	0	0	0	1.1	0	2.2	66.6	77.8
II	No.	64 Bilat. 2	35	21	40	0	13	17	6	8	17	2 Bilat. 7/2	35	39
	%		54.8	32.8	62.5	0	20.3	26.6	19.4	12.5	26.6	10.9	56.3	61.0
III	No.	32	30	23	31	10	14	27	2	1	27	1	2	6
	%		93.7	72.0	96.9	31.3	43.7	84.4	6.3	3.1	84.4	3.1	6.2	18.7
All cases	No.	103 Bilat. 4	69	44	73	10	27	44	8	10	44	8/5,1	44	52
	%		67.0	42.7	71.8	9.7	26.2	42.7	7.8	9.7	42.7	7.8	42.7	50.0

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cancer could not be classified accurately. The final outcome is not known in eight cases but these are listed as dead at the time of last observation. (See Chart I.)

It will be noted that in four cases in the series bilateral carcinomata of the breast were present. In these cases it can not be determined whether or not the disease in the second breast was a metastatic or new cancer. Since these patients were free from the disease for over five years they may be given credit for the period during which they were free; however, in classifying them I have included the individual tumors in all but the mortality statistics.

Ten patients in this series died of diseases which were proven not to be cancer. If they lived for five or more years, and were free from evidence of malignant disease, they are given the benefit of their period of life without cancer. I believe this to be a fair method, especially since the untraced patients are included among the dead.

The cases were grouped according to the extent of involvement. In Group I the patients were free from involvement of the axilla as reported by the pathologist. In Group II there was axillary involvement, minimum skin involvement and the tumors were movable. In Group III the cases were more advanced but still were considered by the surgeon to be operable. It is shown that of the patients in Group I 77.8 per cent are now free from cancer. Of those in Group II 61 per cent lived for five or more years and 56.3 are free from the disease. However, of those in Group III 84.4 per cent died of cancer and only 18.7 per cent lived for five years.

When all of the cases are included as one group it is found that 50.5 per cent lived for five or more years and 42.7 per cent are free from disease for five or more years.

The numerous reports in the literature regarding the results of operation alone for cancer of the breast indicate that not more than an average of thirty per cent of cases so treated are free from the disease after five years. If we compare the results in the series of cases which I am reporting here in which almost 43 per cent are free from the disease after roentgen therapy as an adjunct to operation we must appreciate that fact that there is a decided advantage to be gained by the procedure.

THE TECHNIC OF THYROID SURGERY

Robert S. Dinsmore, M.D.

A discussion of the technic of thyroid surgery obviously precludes any description of preoperative treatment, but it is taken for granted that a careful preoperative regimen has been followed.

A satisfactory technic is one which can be carried out within a reasonable length of time, under some form of light anesthesia or analgesia augmented by local anesthesia, one in which the proper amount of the thyroid gland is removed without injury to the recurrent laryngeal nerve or parathyroid bodies, one in which the result is satisfactory from a cosmetic standpoint, and above all, one which brings about the cure of the patient.

In reviewing the literature on the technic of thyroid surgery, we must conclude that there are many variations of technic all of which fulfill the requisites mentioned above, and that the principles are the same in all, the method varying more or less with the individual operator.

The anesthetic which we use is light analgesia supplemented by local infiltration with three-fourths per cent novocain. The infiltration is carried out in three steps, a small wheal being made intradermally with a fine needle placed at the mid-point of the projected incision line. From this point the novocain is introduced, the skin and subcutaneous tissue being infiltrated over a wide area. No attempt is made to infiltrate beneath the cervical fascia or preglandular muscles. It is important that the neck be placed in extension without any rotation of the head.

A transverse incision is made, no attempt being made to make an elliptical one (Richter). For practical purposes the incision is made at a point midway between the episternal notch and the cricoid cartilage.' We have found that by this procedure the most satisfactory scar is produced. Generally speaking, the unsatisfactory scars are usually too low rather than too high. If an elliptical incision is made, frequently it is observed after the scar has formed, that the ellipse is much more exaggerated than had been anticipated. The incision is made with the head extended backward and when the neck is again in a normal position the transverse incision will give a slightly curved satisfactory scar.

The incision is carried directly through the skin and subcutaneous tissue across the platysma muscle and down to the cervical
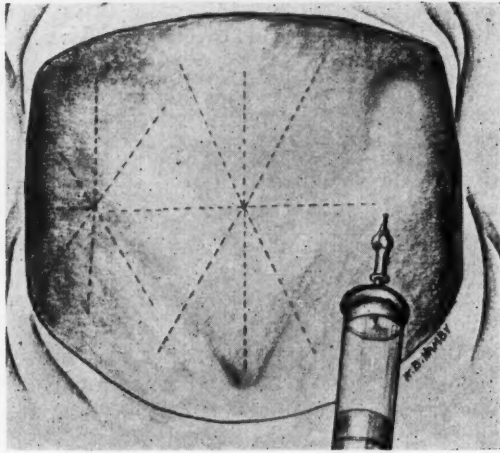
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Fig. 1. With the neck in the proper position, three-fourths per cent novacain is injected into the skin and subcutaneous tissue. No attempt is made to inject beneath the fascia at this time.
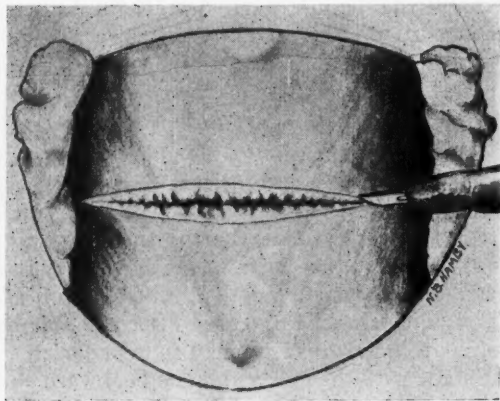

Fig. 2. A straight transverse incision is made across the neck. Dissection is carried through the subcutaneous tissue and platysma muscle down to the cervical fascia, thus giving a full thickness skin flap.
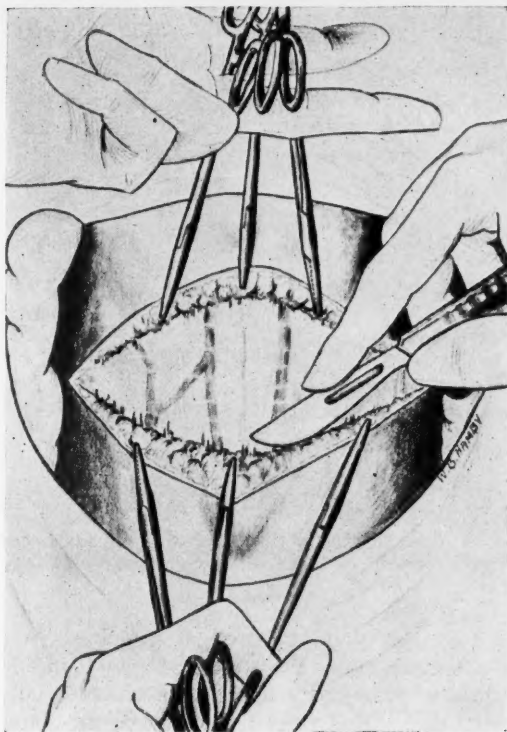
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Fig. 3. The skin flaps are dissected upward and downward, below to the episternal notch and above to the level of the cricoid.

fascia, making a full thickness flap. The flaps are then dissected upward and downward, care being taken to carry the dissection down to the episternal notch and upward to the level of the cricoid. It is essential that the dissection be fairly wide as the preglandular muscles are not divided transversely. This latter practice has been discontinued in our Clinic.

After the dissection of the skin flaps, the second step of the infiltration is carried out, the novocain being injected into the immediate cervical fascia, and the preglandular muscles. After the high and low dissection of the skin flaps it is possible to make a long linear incision through the fascia and preglandular muscles, down to the capsule of the gland which is also divided in the same line and the gland exposed. The capsule is then dissected free and as much
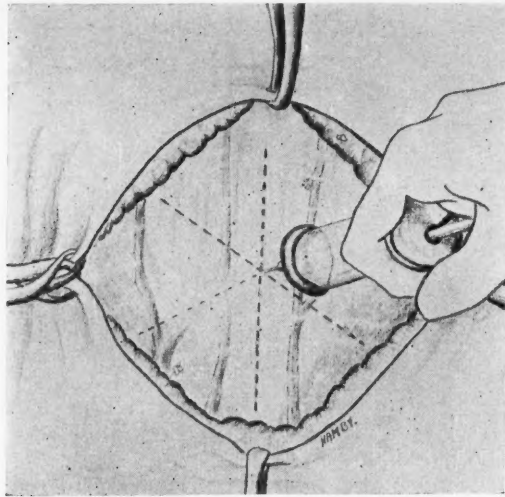
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Fig. 4. After the dissection of the skin flaps, three-fourths per cent novocain is injected beneath the cervical fascia and into the preglandular muscles.

of the surface of the gland exposed as possible. We have tried various sorts of clamps for elevating the gland and have finally resorted to the use of hemostats, three of which usually are used. They are placed just within the true capsule of the gland.

The third step of the anesthesia is the infiltration of the gland itself with novocain. Ordinarily this infiltration can be carried out with from 10 to 15 cc. of novocain the greater portion of which is injected into the superior pole. After the gland has been exposed and infiltrated it can then be lifted up and the superior pole exposed. I prefer to remove the right lobe first, but here again this is simply a matter of personal choice.

Two clamps are placed on the superior pole after it has been lifted up and it is absolutely certain that the upper pole is free from the fascia connecting it with the larynx. Pemberton is always careful of this point and places his index finger beneath the superior pole. This is an important step because the clamps must be applied always from within outward. If the clamps are applied from the outside of the gland it is easy to pass by it and catch the terminal branch of the recurrent laryngeal nerve as it passes into the larynx. This observation is not a theoretical one as I have been unfortunate enough to see it demonstrated in the autopsy room. It is quite true
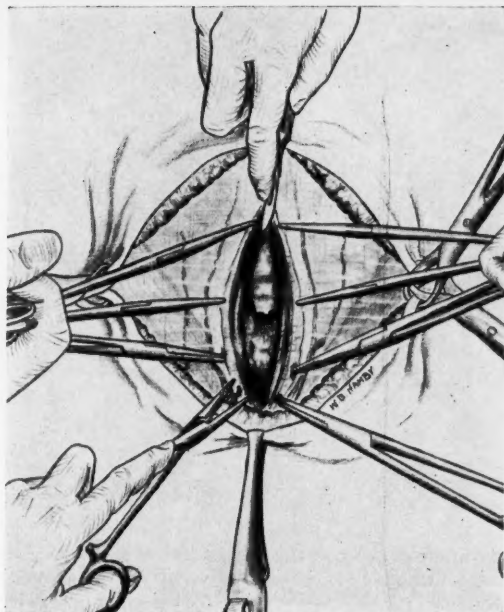
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Fig. 5. A longitudinal incision is made through the fascia, preglandular muscles and the capsule of the gland. This dissection is carried from the level of the cricoid well down into the episternal notch. With a long incision it is not necessary to divide the preglandular muscles transversely.

that the upper pole is not always directly opposite the larynx but in the majority of instances this is an anatomical finding.

A second hemostat is then applied to the lateral vein of the thyroid which is ordinarily at the outer surface at the juncture of the middle and lower thirds of the gland. Hertzler[2] considers this one of the important steps in any thyroidectomy, stating that the line of cleavage is often lost at this point because of the fact that the fascia planes divide here, one sheath going over the carotid and the other to the gland. Guthrie routinely ligates this vessel first. The third clamp is then applied at the inferior pole. I have always made it a point to leave some thyroid tissue at the inferior pole, and I prefer to place the clamp in such a position that after it has been applied it will stand erect in the wound. I think that a great deal of the difficulty with bleeding which is encountered in thyroid surgery can be lessened if these three pilot hemostats are consecutively applied. The poles and the lateral thyroid fascia can then be divided
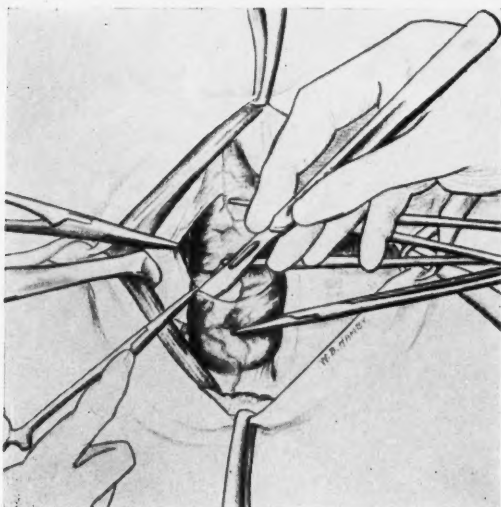
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Fig. 6. The capsule of the gland is dissected cleanly from its surface laterally to the level at which the gland is to be divided. None of the capsule is removed.

and an incision made through the lateral posterior border at the point at which the gland is to be divided. This incision can then be carried in for a short distance, approximately one centimeter. After this has been done it will be noted that the gland can easily be lifted forward. From this point the gland is turned outward and the dissection carried from the tracheal side. Sistrunk always advocated this procedure and it has been a great help to me. The clamps can now be placed nearly transversely above the trachea and the dissection carried from that point outward. This procedure does away with the difficulty of placing the clamps down along the side of the trachea which is directly along the tracheo-esopha-geal groove and is a common site for injury to the recurrent laryngeal nerve.

After the gland has been removed, the tissues are ligated with fine catgut ties. I think it is important that as little sewing as pos-sible be done in the ligation of these tissues as I have seen needles passed around them. In one instance, I was unfortunate enough to pass a needle through the recurrent laryngeal nerve on the right side in the case of one of my own patients in whom a massive collapse of the lung developed on the same side, and death resulted.
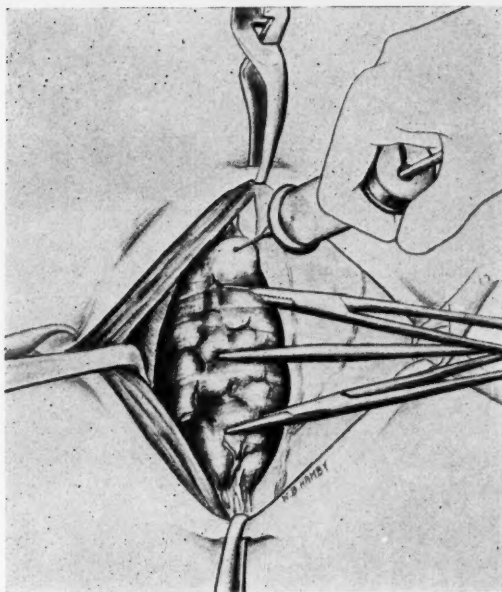
Fig. 7. After the gland has been exposed the third infiltration is made; usually 10 to 15 c. c. of three-fourths per cent novocain injected into the upper pole will suffice.

I prefer to ligate the upper pole with a double catgut suture, inserting it from the same direction as that in which the clamps were applied, that is, from within outward. After the hemostasis is complete the same procedure is carried out on the opposite side. After the ligation has been completed on the opposite side the wound is carefully inspected and the patient asked to cough in order to make sure that the ligatures have been accurately applied. It has been our practice routinely to place a small rubber tissue drain or a small tube in the wound. Recently I have been using a Y-tube the ends of which project into the cavities caused by the removal of the lobes.

An accurate closure following a thyroidectomy is of the utmost importance. One of the most distressing complications is an adherent scar or a small adhesion, which moves with swallowing. This is uncomfortable for the patient and is always noticed by his friends. I have dissected out a fairly large number of these postoperative adhesions and in most instances I have found that they
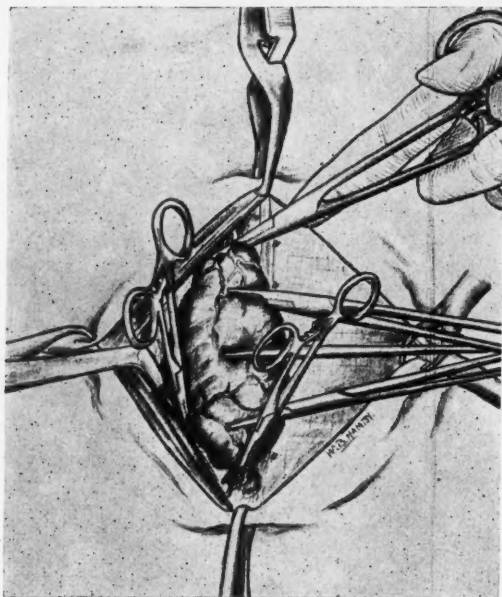
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Fig. 8. After the clamps have been placed in the gland for traction, three pilot hemostats are applied. The upper pole is dissected free and lifted up, the hemostat always being directed from within outward. The lateral thyroid vessels are caught with the second hemostat. The inferior pole is then caught, the clamp being applied so as to take some thyroid tissue with it and to have the clamp standing erect.

are caused by a retraction of the preglandular muscles. After dissecting down to the cervical fascia I have found the fascia to be adherent to the trachea, the muscles having retracted. The correction of this condition is not a simple procedure as a very much wider dissection may be necessary than one would suppose in order to get the muscle and fascial layers again in approximation. All layers are closed separately. Interrupted sutures are placed in the capsule of the gland and the preglandular muscles are then approximated with fine catgut sutures and the fascia is closed with a running suture of fine catgut, a small opening being left near the lower angle of the wound for the insertion of a drain. No effort is made to close the platysma, but the full thickness flaps are closed with skin clips. If a satisfactory scar is to be obtained with skin clips it is quite important that they be placed accurately and inserted directly over the incision line and at right angles to it. It is a very common error to apply these clips from the side so that they appear
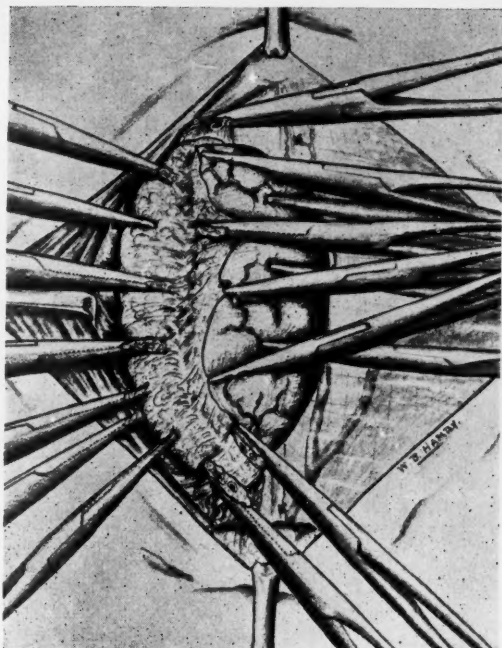
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Fig. 9. After the points within the primary clamps have been divided, the dissection is begun from the outside of the gland and carried inward for about one-third of the extent of the gland.

at many different angles when the incision line is completely closed. The clips should not be applied too tightly and should always be removed in from forty-eight to seventy-two hours to prevent the formation of small scars which may result if the clips are left in place too long.

In my own hands, the technic described above has been the one in which I have seen the smallest number of injuries to the recurrent laryngeal nerve. The most common sites for injury of this type have been the superior pole, the inferior pole, and tracheo-esophageal groove at about the middle point between the level of the inferior and superior poles. If the superior pole is free and the clamps are inserted from within outward I believe that the injury at the upper pole is of rare occurrence. Injury at the inferior pole is also rare if the hemostats are kept within the gland.

After the gland has been divided at both poles and another incision has been made through the posterior lateral border and the
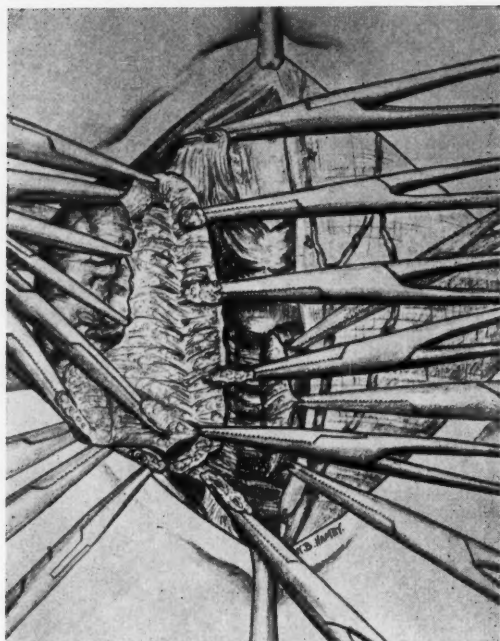
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Fig. 10. After the superior pole, the lateral veins and inferior pole have been divided and the lateral incision into the gland substance has been made, the gland is turned outward and the isthmus divided. The gland can then be lifted well forward, and the clamps applied nearly transversely, that is, away from the tracheoesophageal groove.

gland has been lifted up, the dissection can be carried across the gland in such a manner that a triangular piece of thyroid tissue is always left covering the tracheo-esophageal groove. I do not believe that this can be prevented by complete removal of the gland from the outside inward as it is very easy to rotate the trachea forward, in which case it will suddenly be found that a great deal of thyroid tissue along the lateral surface of the trachea has been removed, and there are small bleeding vessels almost in line with the recurrent laryngeal nerve.

Anatomical studies have shown that the most constant site of the superior parathyroids, is in the posterior capsule of the thyroid gland at the juncture of the upper and middle thirds. The inferior parathyroids lie usually at the juncture of the middle and lower thirds but their location is not so constant as that of the superior
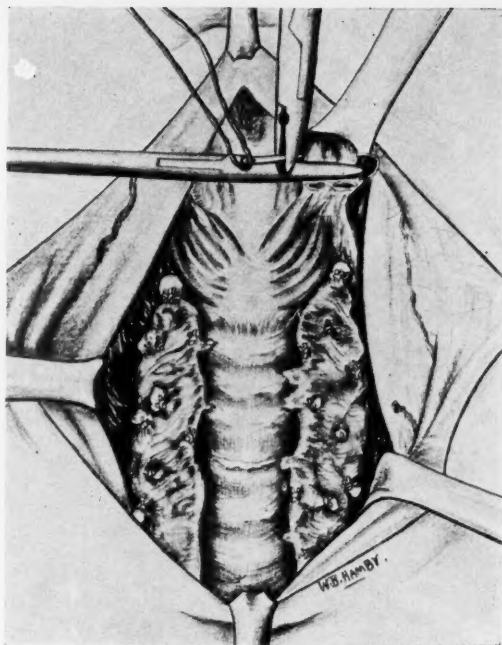
Fig. 11. The upper pole is ligated with a double catgut ligature. The pole is lifted up and the ligature always passed from within outward.

parathyroids. Millzner,[3] Lahey,[4] Terry and Searls[5] have called our attention to the fairly high incidence of the removal of parathyroid bodies which lie on the anterior surface of the gland. This observation coincides with our experience in this Clinic. Graham states that the most common site of parathyroid bodies found in pathological specimens is the lateral inferior border of the gland. Lahey,[4] Searls and Terry[5] have advised the routine search for the parathyroid glands and re-implantation of them if possible.

We have had no experience with the radio knife, although Jackson,[6] Mock,[7] Tinker,[8] and Bartlett and Bartlett[9] have used it. Jackson[6] has summarized the advantages and disadvantages of the procedure, the chief advantages being the time-saving factor, better hemostasis, and less catgut in the wound. He points out that it is especially advantageous in operations on hyperplastic glands and in malignancies of the thyroid. He has pointed out that the radio knife should never be used for the skin incision or near the skin as

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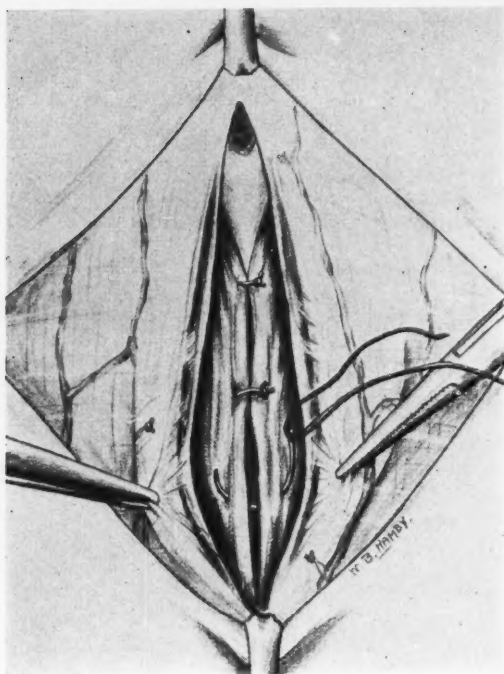
Fig. 12. The capsule is closed with interrupted sutures of fine catgut.

necrosis may result. He feels that it increases the danger of post-operative hemorrhage and that it is of no particular advantage in the case of large adenomatous goiters.

Donald Guthries has made a very pertinent statement in which he says: "One can never afford, even though his experience in thyroid surgery becomes large, to be careless or rough in his operations upon the thyroid gland, nor can he disregard the importance of meticulous postoperative care, for it is attention to these details in the management of goiter patients that spells success."

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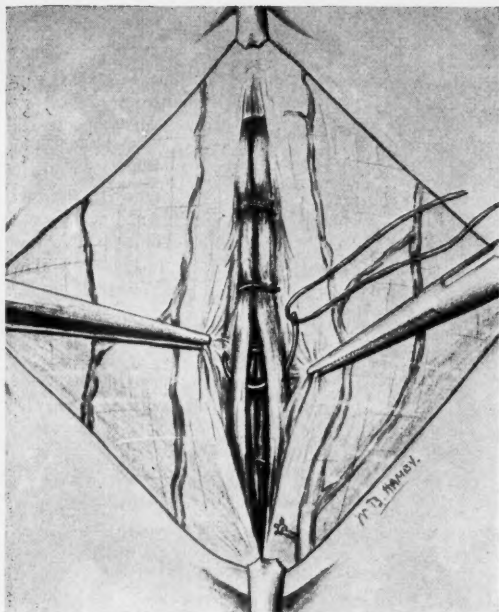
Fig. 13. The preglan-
dular muscles are closed
with interrupted sutures.
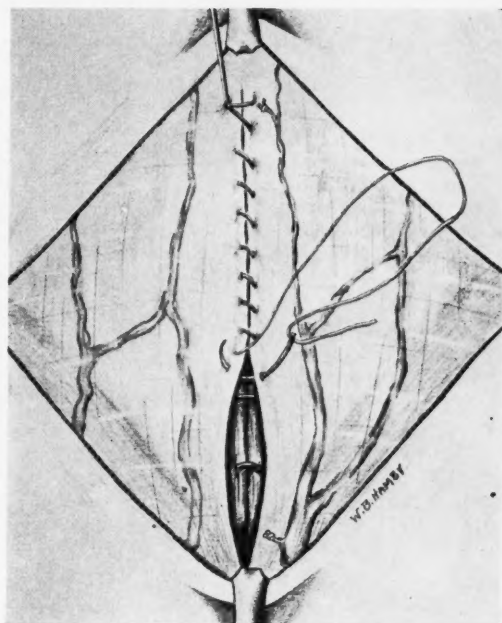
Fig. 14. The fascia is
closed with a fine catgut
running suture leaving a
small opening in the
lower third for the drain.

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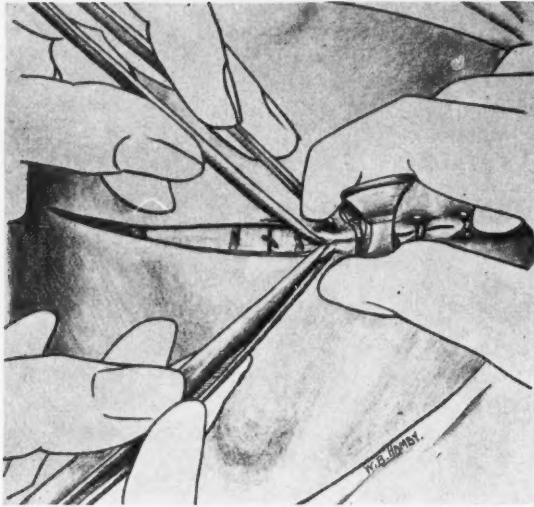
Fig. 15. If clips are used for the skin it is essential that they be inserted at right angles to the incision line. To accomplish this they must be applied from directly above the incision and not from the side, as this invariably leads to a twisting of the clip.

Fig. 16. The wound is drained with a small moulded rubber drain which is removed in from twelve to twenty-four hours.
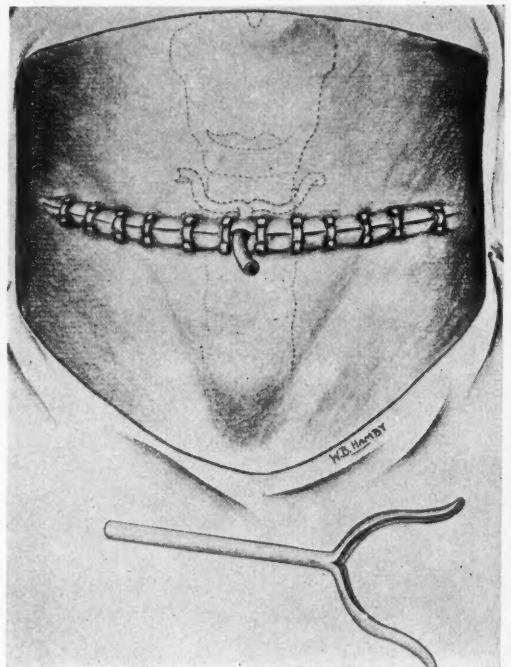
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GENERAL MEDICAL ASPECTS OF ENDOCRINOLOGY

WITH A FEW REMARKS CONCERNING SOME OF THE NEWER
HORMONES

E. PERRY McCULLAGH, M.D.

The following brief review of a few of the interesting features of hyper and hypothyroidism, and hyper and hypoparathyroidism is presented from a clinical standpoint.

Let us consider first some problems in the diagnosis of thyroid disorders.

Three conditions which commonly offer resistance to accurate diagnosis of thyroid disorders are (1) hyperthyroidism in remission, (2) neurocirculatory asthenia, and (3) hyperthyroidism masked as heart disease.

HYPERTHYROIDISM

In recent years, the indiscriminate use of iodin has increased tremendously the difficulty of accurate diagnosis of thyroid disorders. Patients with hyperthyroidism are frequently seen who have been taking Lugol's solution for several weeks, and at the time they present themselves for examination they may have very few symptoms or signs of hyperthyroidism remaining and the metabolism may be normal.

The essential factor in the diagnosis of hyperthyroidism in the case of such a remission is a painstaking history. Usually there is a characteristic onset of the condition with an increasing sense of stimulation warmth, hyperhidrosis, forceful tachycardia, tremor, loss of weight in spite of a good appetite, and distinct improvement after taking iodin. Histories of patients with diabetes or tuberculosis may bear a superficial resemblance to those of patients with hyperthyroidism except for improvement on taking iodin in the case of the latter.

The most important finding from the physical examination is the general appearance of the patient. He is alert, he is apprehensive, the eyes have a brilliant stare, skin is flushed and perhaps a mild hostility may be noted. A similar appearance may be seen in hypertension and at times in beginning psychosis.

The general physical findings may be scanty. A goiter is usually present which may be solid, suggesting diffuse hyperplasia. Mild

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tachycardia may persist. There may be slight cardiac enlargement and usually the heart sounds have a peculiar loudness. The systolic blood pressure often is raised. Exophthalmos is usually absent in the early cases. Occasionally there is a residual tremor and the fine moist texture of the skin may be maintained.

In short, when the history is characteristic of hyperthyroidism, the appearance of the patient is suggestive, and the cardiovascular signs consistent, especially if improvement has been noted following the use of iodin, even though the basal metabolism is repeatedly normal, hyperthyroidism is still present. In such a case thyroidectomy should be performed.

NEUROCIRCULATORY ASTHENIA

Neurocirculatory asthenia is probably misdiagnosed hyperthyroidism more frequently than any other disease. The syndrome is seen usually in individuals under thirty years of age and is characterized chiefly by fatigue, nervousness and vasomotor disturbances.

It is easy to visualize the young woman of twenty whose general appearance as she sits in the consulting room suggests exhaustion. She complains that she is weak and nervous, that she has palpitation on the slightest exertion or even when at rest. She may have been losing weight. She believes a goiter is responsible for these symptoms.

It is often stated that in such a patient nervousness, tachycardia, tremor, hyperhidrosis, weight loss, and goiter are present and indeed the basal metabolism (especially the first estimation) may be elevated. From such a simple statement of facts the conclusion often is arrived at that such a patient has hyperthyroidism. The symptoms and signs, however, must be more critically considered.

The nervousness has probably been present for a long period with slight change, and the appearance of the patient is suggestive of exhaustion. The tachycardia is extremely variable and may change markedly on deep breathing, on ocular pressure, on forceful flexure of the trunk (the so-called Erben's phenomenon) or even on forceful convergence of the eyes (Ruggeri's sign). Tremor is usually coarse.

Hyperhidrosis is present chiefly in the extremities and is associated with coldness. Loss of weight is usually associated with a poor appetite. Goiter, if present, is commonly of the diffuse, soft, so-called colloid type.

In cases of neurocirculatory asthenia the pupils are frequently dilated and may show hippus or positive visero-ocular reflex.

The impressive points in such a case are (1) the prominence of fatigue in the clinical picture, (2) the variability of the pulse rate, and (3) the coldness of the extremities. In such patients even though several metabolism tests may show a rate of plus 16 or plus 20 per cent no hyperthyroidism is present and I know of no type of patient to whom thyroidectomy may do more damage. It is true that in nearly all cases repeated metabolism tests may show a rate falling to normal but this may occur also in mild hyperthyroidism if the patient is at rest.

Hyperthyroidism Masked as Heart Disease

Hyperthyroidism is often misdiagnosed heart disease and patients frequently go about for years with a diagnosis of rheumatic or arteriosclerotic heart disease, with auricular fibrillation or myocardial degeneration, because in cases of mild hyperthyroidism of long standing the cardiac symptoms and signs frequently overshadow all others until they are lost sight of.

In all cases of auricular fibrillation the possibility of the presence of a goiter should be borne in mind as a cause, and in all cases of myocardial damage in which a goiter is present, the existence of the goiter should never be dismissed lightly as a possible cause of such damage, although other signs of hyperthyroidism may not be evident. The so-called "goiter heart" is enlarged to the left, there is increased force and amplitude to the apex beat and the sounds are peculiarly loud. Usually a systolic, non-transmitted, apical murmur is present and perhaps a systolic murmur may be heard at the base. Sometimes a systolic vibration may be felt. A diastolic thrill or murmur is never present. Tachycardia and elevation of the systolic blood pressure may or may not be present.

The history is often suggestive of hyperthyroidism but this may be indefinite. There is no history of rheumatism. Here again the general appearance of stimulation, staring and alertness is important. A goiter is usually present and if the condition is suspected and the basal metabolism is persistently elevated the diagnosis is easy. Not infrequently, however, the basal metabolic rate may be normal in such cases at the time of observation. Such patients are greatly improved by thyroidectomy.

Hypothyroidism

Let me remind you that hypothyroidism is not necessarily present in all cases in which a low metabolic rate is present. Hypo-

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metabolism may occur in chronic exhaustion from various causes, in arthritis, in pituitary disorders, etc.

The results of treatment for this condition would seem to indicate that the diagnosis should be made by a careful correlation of symptoms, signs and metabolic studies.

Hypothyroidism is of especial interest to ophthalmologists, because it is so often associated with ocular muscle imbalance.

Hypothyroidism can seldom be diagnosed by the appearance of the patient. The patient usually complains of lack of energy and endurance, or as he terms it "lack of pep." He may have noted nervousness, coldness, diminished mental alertness and drowsiness or some loss of memory.

Careful questioning may be necessary to reveal further facts. The patient may have noted dryness of the skin and hair, brittleness of the nails, or slight edema especially about the eyes. Paresthesia in hands and feet is frequently noted.

In 100 non-operative cases analyzed recently there was a gain in weight in only 43 per cent, bradycardia in only 39 per cent and a temperature below 98 in 26 per cent.

In the presence of typical symptoms of hypothyroidism a diagnosis may be established although the metabolic rate is not below minus 10. On the other hand, the metabolism may be as low as minus 30 and no hypothyroidism be present. A basal metabolic rate of less than minus 25 per cent, however, is probably due to either thyroid or pituitary disease. In cases in which the diagnosis is questionable a thorough trial of thyroid feeding may be useful. The average dose is 2 grains of desiccated thyroid or 10 grains of the whole gland per day.

Four interesting and common laboratory findings in the presence of hypothyroidism are given below:

(1) Carbohydrate tolerance may be so increased that to produce alimentary glycosuria is practically impossible. Increased tolerance was found in 45 per cent of 20 cases in this series.

(2) Low gastric acidity is often present. Hydrochloric acid was absent one hour after an Ewald test meal in 16 cases of a total of 45, i.e., 35 per cent.

(3) Lymphocytosis of 40 per cent or over occurs in about 30 per cent of cases.

(4) Electrocardiogram showed low amplitude with flat T waves in 16 cases in 58 or 27 per cent. This does not seem to be caused by previous myocardial damage since the amplitude may be made normal on administration of thyroid extract.

CHRONIC POSTOPERATIVE TETANY

In connection with hypoparathyroidism let us consider only chronic postoperative tetany which is due to the removal or destruction of the majority of the parathyroids. The occurrence of this condition may be unavoidable even when standard operative technique is used.

Chronic tetany is characterized by a decrease in serum calcium, a retention of phosphates, intermittent attacks of muscle spasm, and in some cases trophic changes.

The serum calcium is reduced from a normal content of 10 mg. per 100 c.c. to below 9 mg. In some chronic cases the serum calcium has been known to fall to 5.3 mg. per 100 c.c. in the presence of very slight symptoms of tetany. The phosphates rise from a high normal of 4.5 mg. per 100 c.c. to 5 or above.

In many cases the symptoms are for the most part latent; mild paresthesia of hands or feet may be present but may go unmentioned for years.

In other cases more pronounced symptoms appear at the menses, during infection or in exhaustion. In the latent stage Chvostek's sign is usually present. No case has been seen in which Trousseau's and Erb's signs were not present.

An acute attack of tetany is usually preceded by paresthesia in hands or feet; fibrillary twitching and ciliary spasm may occur, then carpo-pedal spasm, hypersensitiveness is present in the extremities; there is spasm of the facial muscles with circumoral pallor; hyperpnoea, laryngeal spasm with stridor, and abdominal pain are noted, and in extreme cases all muscles may be involved. Obviously, motor, sensory, and sympathetic nerves are all involved.

In some cases tetany may occur with extreme suddenness, producing generalized convulsions, usually tonic, but nevertheless frequently mistaken for grand mal. In other cases muscle spasm increases so slowly that walking is interfered with and Parkinson's disease may be closely simulated. Temporary psychoses may occur. The general nutrition of the tissues is poor, the color often sallow, the teeth may be loose, the nails may become chalky white and fall out, and diffuse lenticular haziness may progress to cataract.

The most important reason for thorough treatment of chronic tetany is the prevention of cataract. The patients become so tolerant of low calcium that symptoms are no guide and blood studies must be used.

The most important factor in the treatment of chronic tetany is the giving of large enough doses of calcium. Calcium lactate

powder in doses as large as two heaping teaspoonfuls three to four times per day is usually sufficient. If this amount produces diarrhea, calcium carbonate may be substituted. If calcium alone is not sufficient, lactose in doses of one or two teaspoonfuls three or four times a day should be added, which will help to lower the blood phosphates. If this amount produces diarrhea the dose should be lessened. Milk is useful as it contains both calcium and lactose. Ultra-violet light is helpful. The usual doses of viosterol are of doubtful value. Parathormone may be necessary rarely. In acute cases 5 to 10 c.c. of a 5 or 10 per cent solution of calcium chloride may be necessary. It is best given by the gravity method preceded and followed by saline. Parathyroid administered by mouth has been practically useless in my cases.
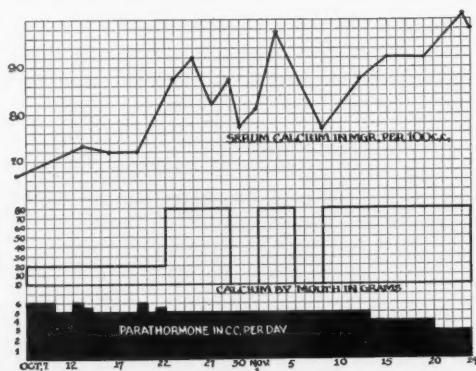
Author's Note — In Chart I "Calcium by mouth in grams" should read "Calcium by mouth in *grains*."

Chart I represents a case of chronic parathyroid tetany and illustrates the value of large doses of calcium by mouth. The upper line represents the total serum calcium which varies from below 7 mg. per 100 c.c. to above 10 mg. per 100 c.c. The lines in the middle of the chart represent the dose of calcium lactate in grains by mouth per day. The lower portion of the chart which is blocked represents the amount of parathormone in c.c. per day. At first the patient was receiving 20 grains of calcium per day and 5 and 6 c.c. of parathormone. The blood calcium varied about 7 mg. per 100 c.c. On October 22nd the parathormone dosage was not changed but the dose of calcium was increased to 80 grains per day. A marked increase in serum calcium followed. When the dose of calcium was decreased the serum calcium fell but rose again when the calcium was increased to the same dose on November 1st. When it was

discontinued, on the 5th day of November the serum calcium again fell but after November 19th it continued to rise following the administration of calcium even though the parathormone was lessened. Subsequently this patient's symptoms were completely relieved by doses of calcium lactate amounting to between 200 and 250 grains per day without the administration of any parathormone.

Chart II represents another case of chronic parathyroid tetany and illustrates the value of lactose in the case of patients in whom the administration of large doses of calcium lactate alone is not sufficient to control the symptoms of tetany. The upper line repre-

sents serum calcium in mg. per 100 c.c. The interrupted line represents the inorganic phosphate of the whole blood in mg. per 100 c.c. The straight black line represents the amount of calcium lactate given by mouth in grains per day and the cross-hatching represents the amount of lactose given by mouth per day. The upper line represents serum calcium; the circle represents the average serum calcium over a nine months' period. The patient was receiving 100 grains of calcium lactate by mouth per day. Between November 12th and March 11th she was taking 200 grains of calcium lactate by mouth per day. During this time the blood phosphates were measured and are reported in the chart. On March 11th in addition to the previous medication lactose powder was given in doses of 120 grains three times a day. It will be noted that the blood phosphates fell following the administration of lactose. During this time the patient's condition very materially improved. The blood calcium was not raised except in the case of the one peak which is unexplained. On April 3rd the dose of lactose was lessened to 180 grains per day and the blood phosphates rose somewhat although they were still within normal limits.
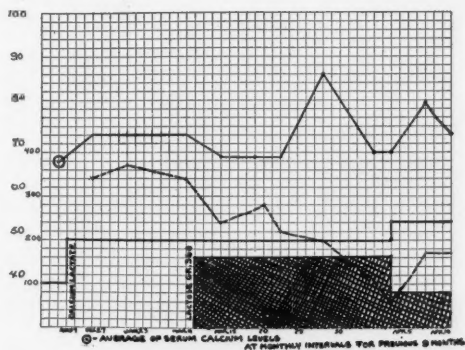
Fig. 1. Photograph showing deformity caused by multiple lesions. The presence of tumors in the left ilium and left maxilla is obvious. Marked deformity of the spine is noticeable and a large tumor is present in the right scapula.

HYPERPARATHYROIDISM

Hyperparathyroidism is a syndrome which is characterized by an increase in serum calcium, a decrease in inorganic phosphates, muscular atonia, general decalcification of bones, and multiple bone lesions. The bone lesions are identical with those known as osteitis

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Fig. 2. Roentgenogram of the pelvis showing the distribution of the lesions present. Areas of rarefaction and cyst formation are seen, especially in the left pubis and ischium, and the left femur and ilium.

fibrosa cystica of the generalized type. There is also diffuse rarefaction affecting all the bones.

The first cases of this type to be reported were all associated with tumor of the parathyroids but more recently cases have appeared in which there is apparently functional overactivity. Usually the serum calcium in such cases is well above 12 mg. and the blood phosphates below 2 mg. per 100 c.c. In cases of long standing this is apparently not always true. This is to be expected since experimental evidence shows that one large dose of parathyroid extract may produce a marked hypercalcemia but if repeated doses are used the calcium may gradually fall to within normal range and the bones become decalcified.

CASE REPORT

A man 31 years of age came to the Clinic with a history of bone lesions which had been known to be present since he was 13 years of age. These lesions involved the skull, vertebrae, sternum, ribs, pelvis and long bones. They were painful and caused much loss of sleep. Fractures were frequent. The serum calcium was above 12 mg. Blood phosphates totaled about 2 mg. X-ray examination of the bones showed the presence of typical osteitis fibrosa cystica. The calcium balance was negative and the blood phosphatase, which is the recently discovered enzyme in the blood which has to do with bone formation and destruction,[1] was increased to ten times the normal.

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Parathyroidectomy was performed and one hypertrophied gland removed. The calcium dropped to normal, blood phosphates rose, phosphatase was decreased to one-third of its original value, the pain in the bones disappeared, strength increased, and no fractures have occurred in a year.

Some of the Newer Hormones

Time will not permit us to consider the pituitary gland but let me remind you of a few facts in connection with some of the more recently discovered hormones. The Aschheim-Zondek[2] test for pregnancy is an important recent advance. As you know, not only an ovarian but also a pituitary hormone appears in the urine in pregnancy. Due to the presence of pituitary hormone, injection of such urine into young test mice produces changes in their ovaries within 100 hours or less which allow of the diagnosis of pregnancy. The result of this test is accurate in at least 98 per cent of cases — more accurate than the Wassermann reaction and probably the most dependable biological test. In the Friedman[3] test similar changes are seen in the ovaries of rabbits after intravenous injection of pregnancy urine. The Mazer-Hoffman[4] test for pregnancy depends on the fact that pregnancy urine, due to the presence of theelin, produces oestrus when injected into castrated female mice.

Folliculin, the follicular hormone of Allen and Doisy,[5][6][7] is on the market under the names of amniotin, estrogen and theelin. Folliculin occurs in urine, amniotic fluid and blood in pregnancy and will produce oestrus changes in castrated animals. Its clinical value is not yet known.

Cortin, so named by Hartman,[8] is the active principle of the adrenal cortex. It has recently been described by Swingle and Pfiffner.[9] Its potency is proved by the fact that it keeps adrenalectomized cats alive for an indefinite period or will bring them from coma to normalcy. Its activity clinically in Addison's disease has been confirmed by Rowntree[10] and others. Recently Roy McCullagh[11] has produced this material in the laboratories of the Cleveland Clinic. It was found to be potent experimentally and in one case in which I tested its action clinically it appeared active although the results obtained were not as striking as those reported by Rowntree.[10]

The male sex hormone may be produced from testes by the method used by Koch and Gallagher.[12] Funk and Harrow[13] have described a method for obtaining it from the urine of young men and animals. Roy McCullagh could not corroborate the work of Funk and Harrow, but working with a different method he found this sub-

stance to be present. The hormone is tested on capons. As is well known, the combs and wattles of castrated young roosters shrink to a very small size. Injection of the male sex hormone in such birds causes these shrunken appendages to grow rapidly. At present we are making a test of the material but are not prepared to make any statements as to its clinical value.

The luteinizing hormone' of the anterior lobe of the pituitary gland may also be obtained from the urine. This substance causes the formation of corpora lutea in the ovary and is apparently active clinically. It lessens menstrual bleeding and evidence is quickly accumulating which indicates that this may be the means of a physiological control of menorrhagia.

Emmenin has recently been described by Collip[14] who believes it originates in the placenta. It is apparently active when given by mouth and causes stimulation of sexual development. Its origin is still debated as it has several properties suggesting its possible origin in the pituitary. Attempts are being made at present to determine its clinical application.

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DENERVATION OF THE ADRENAL GLANDS FOR NEUROCIRCULATORY ASTHENIA

TECHNIQUE AND CLINICAL RESULTS

George W. Crile, M.D.

Based on favorable results of experimental investigations of the adrenal-sympathetic system and on conclusions drawn from operations on the thyroid-sympathetic system in cases of hyperthyroidism, we have sought to control certain analogous energy-transforming diseases, particularly those due to pathological activity of the adrenal-sympathetic system. To this end, we have performed operations on the adrenal-sympathetic system in 126 cases. On this occasion, however, we shall report the results obtained in one group only, namely, cases of neurocirculatory asthenia.

In the war a certain number of officers and men became incapacitated during their service at the front on account of a baffling disorder which was designated "soldier's heart," the principal features being rapid heart beat, nervousness, and fatigue. In the stress of civilian life there are seen many cases of this same condition which is usually given the descriptive name, "neurocirculatory asthenia." This disease resembles, and is often mistaken for mild hyperthyroidism, especially in those cases in which there is a goiter and a moderate increase in the basal rate.

Neurocirculatory asthenia is a pathological state in which there is an excessive stimulation of the adrenal-sympathetic system, and since other kinds of treatment have failed uniformly, we logically concluded that since hyperactivity of the thyroid — hyperthyroidism — could be reduced, then hyperactivity of the adrenals could likewise be reduced.

In association with Dr. E. P. McCullagh, a critical study has been made of the effects of certain operations on the adrenal gland and sympathetic nerves, the basis for these operations being, as stated, the conception that neurocirculatory asthenia is an example of pathological physiology, analogous to the conception that hyperthyroidism is an example of pathological physiology. Jonnesco, many years ago, resected the cervical-sympathetic ganglia for hyperthyroidism — an outstanding example of an attempt to modify pathological physiology. So too, an adrenalectomy performed by

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me 19 years ago, was an attempt to modify certain cases manifesting symptoms of pathological physiology, by surgery. Leriche, of France, Hunter and Royle, of Australia, Adson, Craig and Learmonth, and others are advancing this field of the surgical control of pathological physiology.

About 19 years ago, I first tested the effect of the removal of one adrenal gland in certain cases which manifested symptoms of pathological physiology, in some cases supplementing adrenalectomy by thyroidectomy and resection of the cervical sympathetic ganglia. The results gave promise, but in some cases the good effects tended to disappear in time, just as after unilateral thyroidectomy for hyperthyroidism the clinical results are good at first, then tend to disappear.

After following these patients for a period of years and undertaking new lines of investigation, it was found that a more effective procedure was bilateral denervation of the adrenal glands, the two denervations being separated by an interval of a week or more.

Since we consider that the adrenal glands constitute the power stations or brain of the sympathetic system, and that in neurocirculatory asthenia this power station is pathologically stimulated just as the sympathetic ganglia are too active in Raynaud's disease, we tested this conception by severing the nerves emerging from the adrenal glands.

Our first task was clearly to differentiate neurocirculatory asthenia from a group of diseases which present many symptoms in common. We clearly excluded the diseases analogous to neurocirculatory asthenia, the mechanism of which involves changes in the action patterns in the brain. Among these excluded diseases are psychoneuroses, psychoses, neuroses, hysteria, maladjustments, in short all mental and psychic diseases. We thus limited our attack to that pathologically excessive activity of the adrenal-sympathetic system which produces a classical picture of abnormal nervous excitation, abnormal palpitation of the heart, abnormal nervous fatigue. The analogy to hyperthyroidism is at once apparent, since either the division of the sympathetic nerve supply to the thyroid, or of the adrenal nerves, profoundly modifies the hyperplasia of the thyroid gland, the metabolic rate, and all the symptoms of hyperthyroidism; while on the other hand, abnormal stimulation of the adrenal-sympathetic system easily reactivates the thyroid. That is to say, any one of the several links of the kinetic system may become the site of pathological physiology. This is especially true of the brain itself.

Theoretically, it is clear that pathological physiology of the

· brain can not be relieved by denervation of the adrenal nerves. We have tested this most important clinical point and have found that after adrenal denervation psycho-asthenia, psychoses, psycho-neuroses, oddities of action patterns, and hysteria are not in the lease benefited, just as these psychic and mental states are not benefited by thyroidectomy, by ganglionectomy, etc.

The theoretical and the practical indication for denervation of the adrenal glands is found in those individuals whose mental and psychic mechanism falls within normal range, but whose sympathetic system is under an otherwise uncontrollable stimulation analogous to that present in hyperthyroidism and in Raynaud's disease.

ANATOMY

The technique of adrenal denervation requires a precise knowledge of the anatomy of the adrenal glands especially in relation to their nerve and blood supply, and to their position with relation to other organs (Fig. 1).
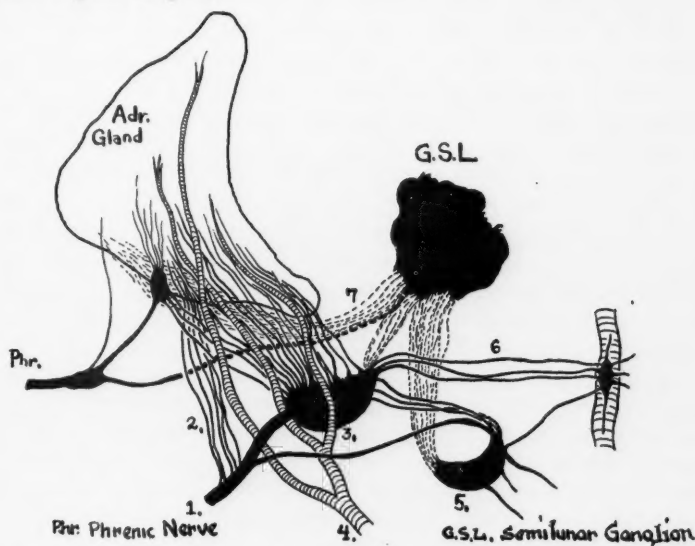
Fig. 1. The anatomy of the adrenal gland. 1, Greater splanchnic; 2, direct fibers of greater splanchnic going to adrenal gland; 3, principal adrenal ganglion; 4, inferior capsular artery; 5, supernumerary ganglion; 6, anastomosis of kidney and adrenal nerves. Note that the solid lines from 3 to the adrenal gland represent the main posterior pedicle. The dotted lines from G. S. L., to the adrenal gland represent the secondary or internal pedicle. (Redrawn from Latarjet and Bertrand, Lyon chir., 1923, xx, 452.)

The adrenal gland is a diminutive yellow pancake, golden in color, soft, friable, and vascular. As indicated by its name, it is situated adjacent to the upper posterolateral aspect of the kidney and always close to the vertebral column. An arrow piercing both adrenal glands would pass approximately through the center of gravity of the body. The gland is held in place by the strands of the sympathetic web, by the slender fibers from the neighboring fascial planes, and by its blood vessels. It is completely embedded in fat, and, on palpation, the adrenal border gives an impression unlike that of any other organ except the external ear to which it is similar in contour and motility.

The right adrenal gland lies in proximity to the diaphragm, the vena cava, the liver, the head of the pancreas, the duodenum, the kidney and the vertebral column. The left adrenal gland lies in proximity to the tail of the pancreas, the spleen, the aorta, the diaphragm, and the spinal column.

When the fascial sheet which binds the kidney to its halo of fat is opened, long blood vessels may be seen passing downward at the side of the kidney toward the vertebral column. These vessels are arrows which mark the trail to the adrenal gland. Generally there is an artery at the outer border of the adrenal and one also at the inner border, the largest artery being underneath, like the stem of a toadstool. From the adrenal glands thirty or more nerves emerge, and these are found on all aspects of the gland except the anterior surface where they appear at the borders.

In hyperthyroidism, the adrenal gland is greatly changed as to its vascularity, its adhesion to neighboring tissue, its appearance, and its texture, just as in hyperthyroidism the hyperplastic thyroid gland differs from the normal gland in respect to vascularity, adhesion, texture, and appearance.

In the course of manipulation incident to the exposure of all aspects of the adrenal gland and to the division of the nerves, oozing and sometimes smart bleeding are encountered. In no case, however, have we found it necessary to tie a vessel because, happily, in this deep operative field clotting is spontaneous. This may well be accounted for by the fact that adrenalin facilitates the clotting of the blood, as demonstrated by Cannon.

Many years ago in researches on blood pressure, I found that, during manipulation of the adrenal gland, an immediate rise in the arterial blood pressure occurred and that immediately after manipulation the arterial blood pressure fell.

I found from these researches that the only gland or tissue in the splanchnic area, the manipulation of which caused a rise in

blood pressure, was the adrenal. The manipulation of every other gland in the splanchnic area caused either a fall in blood pressure or produced no effect.

TECHNIQUE

Except in cases of high blood pressure, spinal anæsthesia is the method of choice for denervation of the adrenal glands, since it produces complete relaxation and lessens bleeding. The alternative to spinal anæsthesia is local and regional block anæsthesia combined with analgesia or with nitrous oxide or ethylene. If the operation is being performed under local and regional anæsthesia, then the adrenal glands, themselves, are blocked with novocain, since, although they lie among tissues which are only slightly sensitive to pain, they themselves are sensitive.

In several cases, with the patient in the prone position on the table, we have made the approach along the lumbar muscles through a vertical incision, believing that in this way we would approach the gland on its posterior aspect and by a shorter route. The special advantage of this method was that the nerves and blood vessels could be seen more directly, but the procedure had limitations due to the position of the patient on the table.

We have also made a vertical incision toward the anterior aspect of the adrenal along the tip of the twelfth rib but this method entailed too much contact with the peritoneum.

Recently, our method has been to make a modified kidney incision. This incision, running from behind forward, terminates at about the middle of the twelfth rib, and is then carried downward vertically (Fig. 2). The incision must be large enough to admit the hand into the renal space. Every bleeding point must be securely tied before the deeper dissection is begun. Since good exposure is essential, by means of a right-angled retractor, the twelfth rib is raised and the bloodless field is disclosed. After the renal fascia has been adequately incised, a long vessel may be seen in the renal fat, the vessel which, as stated above, marks the trail to the adrenal gland. The first step is to mobilize the upper pole of the kidney and to depress the entire kidney when usually the yellow curved edge of the adrenal pancake may be seen. If the adrenal is not seen, the hand is introduced, and by palpation toward the vertebral column and the great abdominal vessels, the external earlike border of the adrenal will be felt. At this point special instruments are introduced — namely, long, slender dissectors at one end of which is a dull dissecting blade and at the other end a blunt hook. In addition, we use a pair of blunt nerve hooks on a long shaft, a pair of French
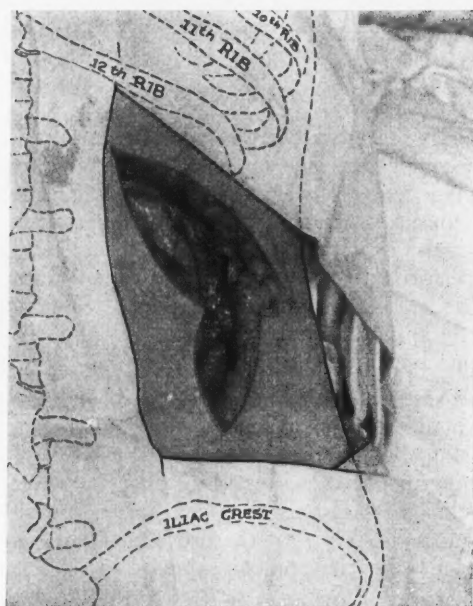
Fig. 2. Incision for denervation of the adrenal gland.

intestinal forceps, a tonsil dissecting knife, a fork retractor, and a pair of curved tonsil scissors (Fig. 3). These special instruments were constructed by Mr. V. B. Seitz, of the Cleveland Clinic.

The softness and brittleness of the gland precludes grasping it in an instrument in order to hold it and orientate its position and also, owing to the nerve and blood vessel attachments, the gland can be moved only within a very short radius. For these reasons the operation must be carried out essentially *in situ*.

After the gland has been exposed by separating the fat, the blood vessels are identified, and then, by means of the blunt nerve hooks, tonsil scissors and a long-handled tonsil knife, the nerves are divided. When this procedure has been completed, the adrenal gland will be quite mobile. It can then be raised up vertically from the vertebral column for a considerable distance.

Owing to the loose retroperitoneal tissue and the danger of oozing, we have usually inserted two cigarette drains, in the lumen of which iodoform gauze has been placed. The iodoform is used to prevent the contamination of the blood serum along the drains
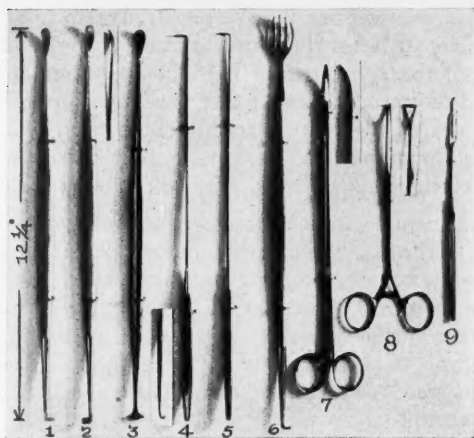
Fig. 3. Special instruments used for denervation of the adrenal gland: 1, 2 and 3, long slender dissectors at one end of which is a dull dissecting blade and at the other end a blunt hook; 4 and 5, pair of blunt nerve hooks on a long shaft; 6, a fork retractor; 7, pair of curved tonsil scissors; 8, pair of French intestinal forceps; 9, tonsil dissecting knife.

from a staphylococcus infection from the skin. The important point to remember is that, in approaching the glands, rigid attention should be paid to land marks and the operating field should be bloodless.

IMMEDIATE OPERATIVE RESULTS

Since the operation is performed in a territory of meager sensory innervation, and the blood loss is slight, there is but little shock. In 126 cases, there have been no deaths from anæsthesia, pneumonia, shock, or hæmorrhage. There have been two physiological deaths, but such deaths are now easily avoidable.

It is most important to state again that the clinical results in cases of diseases of mental or psychic origin, which may be confused with neurocirculatory asthenia, are negative. The differential diagnosis can be made with reasonable certainty by a careful history and physical examination.

The first point in the diagnosis is to make certain that the mental and psychic mechanism is normal. Then if an unstable heart is found, as manifested by tachycardia induced by trivial causes, or by no apparent cause such as by changing posture, by turning over in bed, by standing up, by slowing of the heart rate when the patient

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bends over, by any alterations in the heart beat up to and including paroxysmal tachycardia; if the pupils dilate as the result of pressure on the region of the epigastrium; if hippus, tremors, sweating and cold hands and feet are present, if there are unaccountable nervousness and tremors; if there are intermittent nervous excitation and fatigue; if infections and heart lesions are excluded, then the diagnosis of neurocirculatory asthenia may safely be made.

The heart can not initiate tachycardia, but tachycardia is imposed upon it; so the sympathetic system can not initiate stimulation, stimulation is imposed upon it. Our purpose in these cases, therefore, is to interfere surgically with this pathological stimulation by denervating the adrenal glands, and we are finding the clinical results comparable to the results of thyroidectomy in cases of hyperthyroidism. So also "soldier's heart" could have been relieved by adrenal denervation.

The day following the first denervation the patient will notice a lessening of consciousness of his heart; he will experience a diminution of the feeling of nervous tension; he will observe a lessening of the cold sweat; a warming of the skin; and the nurse will notice that the patient is less restless — a sequence similar to that which is observed after thyroidectomy for hyperthyroidism. If the first denervation produces none of these beneficial results, it will be because the diagnosis is incorrect and the second denervation need not be performed. In correctly diagnosed cases, the second denervation will be followed by further improvement along the same lines, and the general improvement in cases continues steadily, just as in the cases of hyperthyroidism.

Among the inconstant but frequent results is the disappearance of constipation and indigestion.

End-Results

As to the end-results in our cases, 1 patient has remained well for 14 years after unilateral adrenalectomy; 1 for 4½ years after unilateral denervation; and of the 21 cases of bilateral denervation performed within the past 18 months, 18 patients have remained well to date, in 2 cases the results are negative, and 1 patient we have been unable to trace. The final decision as to the potency of adrenal denervation must await the test of time.

SOME PRACTICAL CONSIDERATIONS IN DIABETES MELLITUS

Henry J. John, M.D.

Diabetes no longer presents the economic problem that it has in the past. Before the era of insulin, diabetic patients were a great liability. Usually patients with 'severe diabetes were a hopeless burden to their families or to their communities. [Those of you who have treated diabetics for as long as 11 years, know well the problems that 'severe diabetes presented. Treatment by starvation, the only method available in those days,' was anything but pleasant for the physician, as well as for the patient.

Today in this country there are nearly two million patients with diabetes in various degrees of severity. They are no longer a great liability, but, for the most part a definite asset to society. A diabetic patient no longer has to starve himself, he no longer has a dreary outlook on life's progress, he no longer has the fear of early death. Quite the contrary, he may have a liberal diet, his outlook on life is cheerful, he accomplishes as much, if not more, than the fellow who has no diabetes, and, as has been shown by statistics, his life span is longer than that of persons without diabetes. In the history of medical diseases the chapter of diabetes reads like a fairy tale. Such rapid progress seems almost unbelievable.

The routine treatment of diabetes is so well known and so well standardized, that I shall spend no time discussing it. The basic principles of the regimen are described in any standard work on medicine. A clear understanding of the details in the treatment of diabetes comes only from prolonged work and experience in the field. In the future I feel but little progress will be made in treatment. Certainly I look for no radical changes. Where tremendous progress will occur, however, is in prevention and in the treatment of juvenile diabetes. Today these present the most interesting problems and the most promising fields for clinical investigation. Our future milestones of progress will be marked by the children afflicted with diabetes. For that reason, the treatment and the study of diabetic children ought to be restricted to fewer men, so as to give them an opportunity to gain a wider experience and to exert a more concentrated effort in order that progress in this special field may be more rapid. There are relatively few diabetic children and if many different doctors are treating them, further progress is likely to be retarded.

Before discussing the prevention of diabetes, I want to stress the importance to the patient of the early recognition and early treatment of the disease.

The importance of early treatment. With all our studies and efforts at prevention diabetic patients will always be with us. By the methods of prevention we can hope only to reduce the total number of diabetics. Inasmuch as diabetes is and always will be a medical problem of considerable extent, an effort should be made to discover the disease in its incipiency. To discover and to treat tuberculosis in its incipiency is well recognized as *the* orthodox procedure, the only procedure which brings good results. With diabetes there is identically the same problem. Discover it in its incipiency and you will have done a valuable service to your patient, for you will have a splendid opportunity to prevent any further destruction or dysfunction of the islands and keep his diabetes in a mild stage. Those islands that are gone can not be replaced but those that are still present can perhaps be saved; that is the medical problem confronting the physician at any stage of diabetes.

Upon finding a trace of sugar in the urine, especially in a young or middle-aged patient, it is wrong to leave it at that, to wait until much sugar appears, or to tell the patient just to cut down a bit on sugars and starches. Such a patient needs further investigation and a definite solution of his problem. It may be the beginning of diabetes or when his problem has been worked out it may be found that he does not even have diabetes. Having no laboratory facilities is no excuse, for there are plenty of laboratories and plenty of well trained medical men who will gladly work out the problem and give their data and their advice. I am emphasizing this because I meet with this situation frequently. Patients today usually are keen and wide awake and with just a spark of suspicion they may look for help elsewhere. And how easily the physician can eliminate this very thing and protect himself. Repeatedly I have seen patients who have been treated for diabetes, from one month to two or three years, and finally when the case was studied thoroughly it was found that they did not have diabetes. Or again, I have seen patients whose diabetes definitely began a year or so before with no treatment in the interim, and by the time I saw them they had severe diabetes which necessitated strict diet and insulin. Perhaps a year before, when the diabetes was just starting, they might have been treated more economically and more efficiently with a milder regimen.

It is well not to wait for the development of the classical symptoms of diabetes. They are present in a comparatively small per-

centage of cases and if they are taken as criteria the majority of diabetics will have been missed. The early cases have practically no symptoms of any significance. These come only at a more advanced stage of diabetes. If the diabetes has been developing gradually the symptoms will not appear at all, for the body has had ample time to readjust itself to the new state of affairs. The symptoms do come if the onset is rapid, and the rise of blood sugar overwhelming, for in such a case the body has not had time for physiological readjustment and most or all the classical symptoms will be present. Or symptoms will appear in a case that has been evolving gradually when an acute infection of some sort, tonsillitis, carbuncle, influenza, super-imposed on the slowly developing diabetes rapidly raises the blood sugar and produces acidosis. Such a patient may even go into coma within 24 hours.

At the Cleveland Clinic we do routine blood sugars in all new cases. The percentage of patients with unsuspected diabetes, dis-covered in this manner is considerable. You can imagine how chagrinned a physician feels when he has taken a careful history and has done a thorough physical examination and has sought the counsel of one or more specialists for whatever seemed indicated, and then a blood sugar report of 380 mg. per 100 c.c. comes from the laboratory. This settles the problem of diagnosis, yet when the history is re-examined, there is not an inkling of a symptom or a complaint which would even suggest diabetes.

Just as I wrote this such a case came to my attention at the Clinic. The patient was a man 64 years of age, who came in for an entirely different reason, and diabetes was not suspected until the laboratory report appeared. Two more such cases appeared the next day. One of the most striking cases that comes to my mind was that of a young girl, 16 years of age, whom I saw in coma three years ago. In going back over her history, there was not an inkling of a symptom which would make one think of diabetes. And yet she went into coma within 24 hours, following an acute gastro-intestinal infection.

Many of these patients with a very high level of blood sugar do not have glycosuria. It is not uncommon to see the blood sugar as high as 200 mg. to 300 mg. per 100 c.c. without accompanying glycosuria. The highest value for blood sugar without glycosuria that I have seen was 552, a figure which is, of course, exceptional.

Whether or not sugar will appear in the urine at any given time depends entirely upon the renal threshold for sugar of the particular person. This renal threshold is not fixed, but varies widely in dif-

ferent individuals and perhaps slightly in the same individual. The renal threshold is high in the obese, and there is also a step-like rise of thresholds in various affections. I do not mean to imply that these are fixed figures, for these are but average values; in each group there is a wide range up and down. The diabetics have the highest threshold of all. This may be a protective mechanism of nature's to prevent more sugar from being excreted.

For that reason the clinical course of diabetic patients who have a high renal threshold can not be followed well by urinary examinations alone. In treatment an effort is made to approach as nearly as possible the physiological type of glycemia. Hyperglycemia is not physiological. Diabetic patients who have a low threshold can be guided even less by the urinary examinations, as they will show a more or less constant glycosuria. It is in the middle group of patients in which guidance and follow-up may be accomplished by urinary examinations alone. But in order to know to which of the three groups any given patient belongs, one has to work out the problem of the patient's renal threshold. For a quick and practical answer to a man in general practice this is of little help. This just shows the problems involved in the treatment of diabetes. I do not mean to be discouraging, for, after all, good work in the treatment of diabetes was done when no studies of blood sugar were available. And good work can still be done, though the availability of blood-sugar studies improves the situation. If one is dependent upon urine examinations alone, one should examine the 24-hour specimen of urine and compare the subsequent examinations in order to see whether the 24-hour output is diminishing or whether it is increasing, so that one can alter the treatment accordingly. Even a better way is to examine each specimen of urine during the 24 hours in order to see at what time during the day the patient is losing sugar, and when his urine is sugar-free. In this manner, if insulin is used, the dosage can be adjusted more closely. The examination of a single specimen of urine, taken at random, is of very little value.

Prevention. By the prevention of obesity and infections, much can be done to prevent the development of diabetes. As compared with this, the treatment of diabetes plays but a secondary role, and is but a mere palliative measure. Prevention presents a challenge to accomplish something constructive. The symptomatic treatment of malaria *did not* solve the problem of malaria. The elimination of the mosquito was not treatment; but it *did* solve the problem of malaria!

Obesity. In the studies of men devoting much of their time to diabetes much stress is laid on obesity. In the report of a series of

2,000 diabetics that I published in 1930,' 76 per cent were over-weight either at the time I first saw them or previously. The number of patients with obesity increases with each decade and is most marked in the fourth, fifth and sixth decades; in the last two decades including nearly 90 per cent of those in this age group. The average number of those overweight among patients with diabetes which developed in the fourth decade or later was 79 per cent. The contrast in the percentage of obesity in diabetics and in normal persons is very striking, as can be seen in Chart I, where these two groups are projected side by side according to decades; the figures were obtained from life insurance statistics.
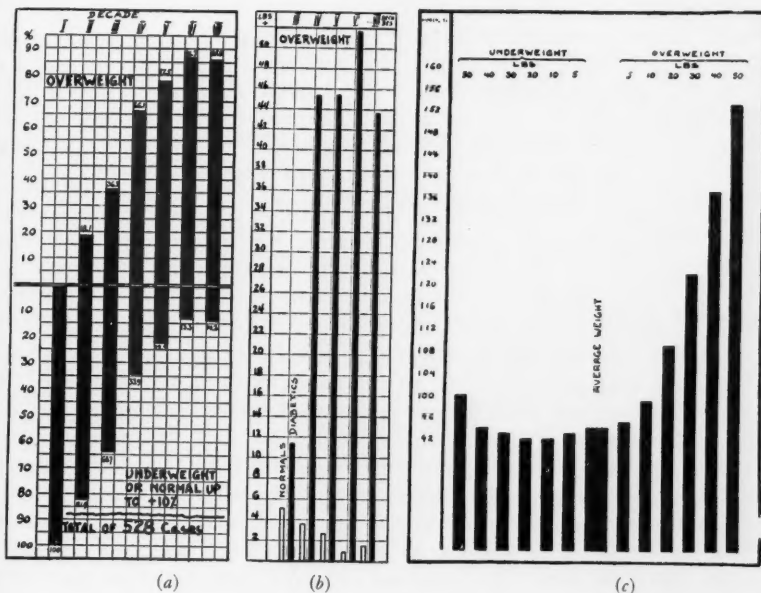
Chart I. (*a*) The relation of overweight according to decades in a series of 528 diabetics. (*b*) The relationship of obesity in diabetics (black column) arranged according to decades as compared with a large series of non-diabetics in these same decades taken from life insurance statistics. (*c*) The relation of weight to the mortality rate.

This is an illuminating picture and it has significance other than just in diabetes. Obesity leads to general diseases due to metabolic degeneration, such as arteriosclerosis, myocarditis, hypertension, chronic nephritis, et cetera. All of these tend to shorten the span of life. In Chart I also is the information on longevity and over-

weight as given by life insurance statistics. These facts are striking, for it is known that the life insurance companies are particular in the evaluation of their risks, and in the study and elimination of physical factors which might shorten the life span. Therefore, this information which they offer us is important since it deals primarily with only the one factor, overweight. Note on the chart how the mortality rate is unaffected by underweight which is shown to the left of the normal standard in the middle. However, when extreme undernutrition is reached, there is a slight increase in the rate of mortality. But look to the right and see the effect of increased weight and its progressive rise of mortality. This needs no comment; the data speak for themselves.

Obesity presupposes overeating. Newburgh in his recent study of obesity[2] makes the following drastic statement: "There is no specific metabolic abnormality in obesity. All obesity is "simple obesity." The increase in weight merely represents an inflow of energy greater than the outflow. Failure of the primitive instinct to adjust the inflow of energy to the bodily needs is always the immediate cause of both leanness and obesity."

What practical relationship, then, has obesity to diabetes? Already I have called attention to the great amount of obesity accompanying diabetes. If obesity is due primarily to overeating, these persons have been placing a great load on the insulogenic function of their bodies. Increased amount of food calls for an increased output of insulin. An increased output of insulin can be provided as long as the insulogenic apparatus is intact, functioning well and maintaining a great reserve. But suppose that an individual was born with an insulogenic apparatus which had not an unlimited reserve; or suppose that an individual was born with a perfectly functioning pancreas, with good reserve, which had been diminished through infections; or suppose that through sclerosis of the vessels, the blood supply to the pancreas had been diminished and a certain atrophy of the islets, either anatomical or functional has resulted, reducing thus the reserve of the insulogenic function. By overeating, and thus placing a big load on such a handicapped organ, it is easy to see how a reduced reserve could be lessened further with the ultimate development of diabetes. This point should be borne in mind in dealing with all types of obesity, for here is an excellent field in which to practice preventive medicine and to reduce the incidence of diabetes.

In a series of 1100 glucose tolerance curves that I published[3] in 1930, 65.6 per cent of cases of obesity in a series of 297 investigated showed a diabetic type of a curve. This fact is even more striking

when we compare the carbohydrate metabolism in obesity cases to that in a group of patients who are not overweight. There are two and a half times as many diabetics among the obese as there are among the lean. The renal threshold in obesity is relatively high, as has already been stated, so in order to investigate the status of an obese person in relation to diabetes, examination of the urine for sugar is not sufficient, but one must resort to blood sugar

TABLE I

The Results of Glucose Tolerance Tests on Obese Patients and Those Presenting Normal Weight

	Type of Curve		Number of Cases	Total	Per Cent	Total Number Cases
Obesity	I, II	Nondiabetic	16, 43	59	34.3	172
	III, IV	Diabetic	23, 90	113	65.6	
Normal Weight	I, II	Nondiabetic	92, 121	213	74.2	287
	III, IV	Diabetic	24, 50	74	25.8	

studies. Whether or not a rise in the renal threshold for sugar means chronic nephritis, is a problem which the pathologists will have to answer.

Hypertension develops more frequently in the obese. In a study of hypertension in various diseases it was found that there is an increase of blood pressure in 42 per cent of the obese; only in carcinomatosis and in hyperthyroidism is there a higher incidence of hypertension. The influence of obesity may be seen even in the group with hyperthyroidism, for when the obese hyperthyroid patients are separated from the lean ones, the incidence of hypertension is again higher among those who are overweight.

Infection. Infections probably play a greater role in the causation of diabetes than we think at present. Though clear-cut evidence of any factor in question is an excellent prerequisite for scientific work, tangible evidence is not always available. Not all medical problems can be solved in a test tube or in the laboratory. A certain amount of philosophy and deductive logic is necessary. Long experience makes such deductions more tenable. All of you, no doubt, have had a "hunch" at the bedside that the fate of the patient before you would be thus and thus; yet were you pinned down to actual facts, you could not explain it in scientific terms. Experience

has taught you, you will say, but more than that is in obscurity. It is on such authority that I say that infections play a considerable role in the development of diabetes. We all see patients whose diabetes followed some infectious disease, such as influenza, pneumonia, cholecystitis, or, in children, mumps, measles, or tonsilitis. In such cases, one can't help but feel that there is a definite connection between the diabetes and the infection.

Let me tell you of a concrete example: A little boy eight years of age, was much emaciated when he was first admitted to my care at the Cleveland Clinic. His blood sugar was 288 mg. per hundred cubic centimeters and he weighed 38 pounds. (Normal weight at his age would be 55 pounds). He gained practically 10 pounds in weight during his stay in the hospital. As much as 35 units of insulin per day had to be used and he was discharged from the hospital after a stay of 23 days with advice to use 25 units of insulin per day. A month later this was reduced to 10 units per day and in less than three months from the time I first saw him, all insulin was discontinued, and he was allowed to increase his diet to 2000 calories, as you will note from the chart. Three weeks later he developed measles. He lived in a small town and the family physician did not realize the havoc wrought by infections in children with even mild diabetes, and hence he did not appreciate the importance of administering insulin at that time. When I saw the boy two weeks later his blood sugar was 497 mg. per 100 c.c. The resumption of treatment with insulin and reduction of the diet was necessary. The dosage of insulin had to be increased up to 80 units per day (in four doses) and the entire course of treatment had to be repeated. The infection resulted in definite damage to the pancreas, for even today — two years later — the boy has to take 27 units of insulin per day. I believe all this might have been prevented by the timely administration of insulin when measles first developed.

A diabetic child should be watched closely when an infection begins, for then more insulin is required temporarily, to protect him from a downward course. If the child's diabetes ordinarily is controlled by diet alone, he requires some insulin, the amount depending on the severity of the infection. Only in this manner can a diabetic child go through an infection safely, without a decrease of his tolerance for carbohydrates. Even such a simple problem presents, then, a fertile field for preventive medicine and gives the physician an opportunity to do constructive work.

The deleterious effect of infection is evident not only in children, but also in adults. I present the case of an old man now 76 years

of age. I am presenting to you the influence of infection in the two extremes of life. This man had always been in good health. In 1919 prostatectomy had been performed and he had made an uneventful recovery. Several urine examinations in 1922 did not reveal the presence of sugar. In 1923 epidydimitis developed, and no sugar appeared in the urine subsequent to this, nor yet in 1924. In February, 1926, there was a slight rise of blood sugar to 149. When this was rechecked a month later it was 114 — normal.

It might be questioned whether this slight rise in the blood sugar was a warning or of no consequence in a man seventy years of age. Undoubtedly it was a warning, for ten months later heavy glycosuria developed with a blood sugar of 400, and the patient had frank diabetes. Could his diabetes have been prevented by mild restrictions in diet had not the original rise in the blood sugar been disregarded? I feel rather certain that it might have been, especially in the light of subsequent happenings.

The patient was hospitalized for two weeks; he was given insulin and a low carbohydrate diet, and his blood sugar returned to normal. When he was discharged he was not taking insulin and was taking a fairly liberal diet. For some years he was quite well and on each subsequent examination his urine was free from sugar and the blood sugar was normal. In January, 1930, when the patient was seventy-four years of age, cystitis developed. Again the diabetes came into the foreground, requiring the routine measures for control. Even yet, this man needs a small amount of insulin, five units twice daily. This case illustrates again, just as in the previous case, what infection does.

It is likely that a similar thing, i.e., loss of some insulogenic function, happens to all of us with any serious infection. This, however, is of small concern, if we have adequate insulogenic reserve, which can not easily be exhausted. It is only when such a reserve is small that diabetes can and does develop.

This premise can be evolved still further. Presupposing a good insulogenic reserve; one infection reduced it; a second infection reduces it more; a series of subsequent infections reduce it still further, until the dividing line may be reached where only one more infection may bring about diabetes. That next infection may or may not take place and consequently the person may or may not develop diabetes. In such a borderline case there are two further possibilities. Such an individual may be just a moderate eater and keep his weight normal, or he may live well and become obese. In the first instance he will stay a borderline case the rest of his life;

whereas in the second, he will break down that small reserve and become a patient with diabetes. It is the last straw always, which breaks the camel's back.

The same reasoning may be applied to the question of hyperthyroidism. Why is it that some hyperthyroid patients do develop hyperglycemia, glycosuria, diabetes? It is not the stress of hyperthyroidism alone which brings it about, for were it this factor, diabetes would be seen principally in the most severe cases of hyperthyroidism. This is not the case, however, for diabetes often is encountered in the mildest cases of hyperthyroidism. In these cases the added strain of hyperthyroidism again happens to be the last straw. Diabetes in hyperthyroidism is not an academic phantom, but a reality. In 9,000 cases of thyroid disease seen at the Cleveland Clinic, 620 cases of 6.88 per cent showed some degree of nonphysiological hyperglycemia. When followed for a period of one to ten years, it was found that most of them improved, but 200 of these 620 patients remained diabetic after thyroidectomy. Over one-third of this permanently diabetic group are still taking insulin in order to control their diabetes. Thus, although 6.88 per cent of patients with hyperthyroidism showed evidence of disturbed sugar metabolism the incidence of actual diabetes in thyroid disease was only 2.1 per cent.

Glycosuria in gallbladder disease occurred five times in 16 cases, that is, in 31 per cent. In this same series, nonphysiological hyperglycemia occurred in six instances at some time or other. In this same group of patients, nine, or 56 per cent, had a normal glucose tolerance curve and seven, or 44 per cent, had a diabetic type of curve.

This shows the relationship of chronic infection to diabetes. The incidence of diabetes in this group is quite heavy. In this group of patients with gallbladder disease it is interesting that the incidence of diabetes rises in succeeding decades. Thus we find in the fourth decade, 20 per cent, in the fifth decade 44 per cent and in the sixth decade 84 per cent with the diabetic type of curves. This suggests that the effects of a prolonged infection, together with physiological wear and tear, finally break down the reserve and results in diabetes. It points also to the need of removing all foci of infection in diabetic patients, whether these be in the tonsils, in the sinuses, in the teeth, in the prostate or in the gallbladder, in order to stop progressive damage within the pancreas.

Surgery in Diabetes. Operation in the presence of diabetes no longer presents the dreaded problem to the surgeon that it did in

TABLE 2

The Mortality of Operation in the Presence of Diabetes in the Pre-insulin Era

	Year	Number of Operations	Mortality, Per Cent
Berkman	1915	26	7.6
Binney	1916-1923	32	19
Bruce	1914	...	50
Bruce	1927	4	0
Chovannez	1925	...	40
Cumston	1914	6	16.66
Fisher	1914	86	48.4
Fitz	1918	45	30
Foster	1925	...	45
Gardiner	1922	25 (Amputations)	80
Jones	1923	8	25
Joslin	to 1917	27	18
Joslin	1919	61	9
Karewski	1914	68	11.8
Lahey	1916	14	7.1 (Thyroid)
Mason	1916-1924	101	18
Mayer	1914	...	54.6
Menninger	1925	47	42.5
Morrison	1896-1913	775	23
Mugind	1921	5	80
Noble	1903	...	24
Phillips Phillips }	1902	101	27
Pilcher	1910	...	50 (Amputations)
Strouse	1916	38	31
Tuffier	1914	...	40
Weeden	1897-1922	160	36.8
Young	1918-1922	99	16.1
		1,728 Total	31.3 Average

the preinsulin era. Today a diabetic patient can be operated on with reasonable safety, provided he is given proper care. Whether this care is rendered by the surgeon or the internist is immaterial. The surgeon, however, is not likely to deal with the medical problems of the diabetic frequently, and, for that reason, he is wise to lean upon the wider experience of the clinician who is well versed in this field.

In the preinsulin era the surgical mortality in diabetes as shown in Table 2, amounted to 31.3 per cent. The ranges in this table are from 0 to 80 per cent. In reality, I believe, the mortality was even higher for there must be much unpublished material. It is discourag-

TABLE 3

Surgery in Diabetes in the Insulin Era

	Year	Number of Operations	Mortality, Per Cent
Adams and Wilder................	1924	327	1.2
Bauman.........................	1925	56	26.7
Bazin..........................	1930	73	2.7
Bruce..........................	1927	97	2.1
Cohen..........................	1923	8	14
Coler and March................	1925	65	24.6
Eliason and Wright..............	1926	55	41.8
Foster.........................	1925	103	11.6
John..........................	1921-1925	35	8.5
John..........................	1925-1928	276	4.3
John..........................	to 12/5/30**	462	4.7
Joslin.........................	1923	69	5.7
Joslin.........................	1924	75	14.6
Joslin.........................	1925	97	10.3
Joslin.........................	1926	81	14.8
Joslin.........................	1927	321	11.5
Judd..........................	1926	667	3
Lemann........................	1926	43	2.3
Mason.........................	1925	101	17.8
McKittrick and Root............	1928	80	11.2
Menninger.....................	1925	22	4.5
Petty..........................	1924	31	12.6
Rabinovitch*...................	1930	130	5.3
Reed..........................	1929	43	25.5
Roth..........................	1926	20	10
Weeden........................	1924	12	1.2
		3,349 Total	11.3 Aver.

*Verbal report. **Unpublished.

ing, to say the least, to publish statistics showing a high mortality rate and no one likes to write about discouraging data.

Since the advent of insulin, data gathered from the world literature in Table 3, show that the average surgical mortality has dropped to 12 per cent. This means that on the average, where three patients died in the preinsulin era, only one dies now. A splendid record for just a decade, and as time goes on I venture to say that even this average of 12 per cent will be diminished considerably and approach quite nearly the surgical mortality in non-diabetic patients.

Such progress is encouraging, not only to the physician but to the patient as well, for it removes the dread of operation which in previous decades could not be avoided. As a result, more and more

diabetic patients are being operated on early and not as a last resort. This too has some bearing on the reduction of the mortality rate.

The treatment of the diabetic who has had an operation is exactly the same as that of the ordinary diabetic, that is, dietary control or dietary control plus insulin. Patients who are ill and can not tolerate food by mouth, are supplied their nourishment through the intravenous administration of glucose to which a sufficient amount of insulin is added to insure the utilization of this glucose. In this way, a patient may be kept comfortable for days, even weeks, at a time, without food by mouth.
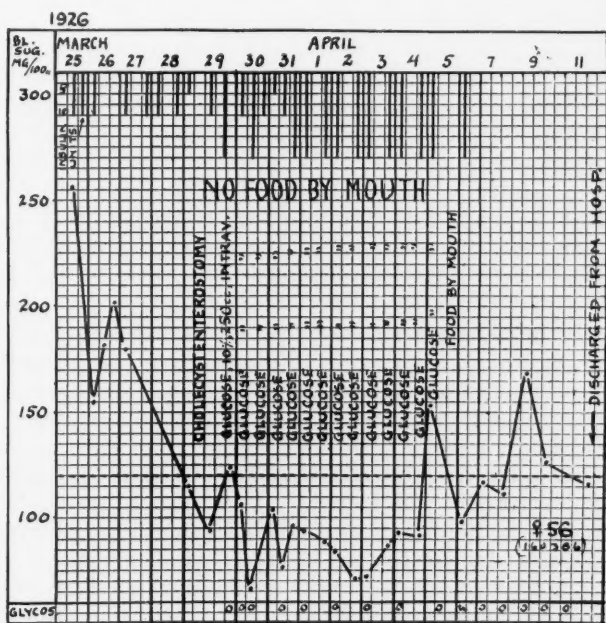
Chart II. The progress of a case of jaundice associated with diabetes mellitus before and after operation; no food was given by mouth for seven days.

Chart II shows the results of this postoperative procedure in a woman 56 years of age who had had a cholecystenterostomy. In order to eliminate peristalsis which might interfere with the healing, she was given 250 c.c. of 10 per cent glucose together with 20 units of insulin twice a day for seven days. During this time she was quite comfortable, there was no hunger, and she made an uneventful

recovery. The administration of glucose did not raise the level of the blood sugar at any time and the urine was sugar-free. When some time ago I went over the data relating to intravenous administration of glucose in diabetics, I found the following: Of a total of 54 cases, 81.5 per cent showed a fall of blood sugar two hours after its administration; 3.7 per cent showed no change in the level of blood sugar; 14.8 per cent showed a rise of blood sugar. The average fall of the level of the blood sugar was 29 mg. per hour; the average rise of blood sugar was 19 mg. per hour.

A diabetic patient should be prepared for the operation, that is, his diabetic condition should be under control and his sensitivity to insulin ascertained. However, in cases of emergency, operation may be done immediately provided the medical man cooperates with the surgeon. A small dose of insulin is given before the operation and the blood sugar, acetone, and carbon dioxide estimations are done (it takes but 25 minutes) while the patient is on the operating table. If the level of sugar is high, another small dose of insulin is given while the patient is undergoing operation. Immediately following the operation, treatment is instituted with insulin, hypodermoclysis, and also glucose intravenously if indicated. It is wise to obtain sufficient laboratory data during the first two or three days; this insures safer and more adequate treatment with better results.

Chloroform as a general anesthetic no longer is used in this country. It injures the liver, causes hyperglycemia and acidosis and for that reason is contraindicated in diabetes. Ether is not much better, especially because of the postoperative nausea which it causes. Nitrous oxide is a preferable general anesthetic. More and more, however, the surgeons are turning to local and lumbar anesthesia and the results are very promising. Just what ether narcosis does to the blood sugar has been shown by experiments on rabbits, which have a parallel in man. The higher curves of blood sugar indicate deeper narcosis. Not only does the blood sugar rise during ether narcosis, but there is a concomitant increase in the ketone bodies which, in a diabetic patient, is undesirable.

Another very helpful thing in the postoperative care of diabetic patients is the early use of the oxygen tent when this is indicated in cases of anoxemia. It should be used before the patient becomes definitely cyanotic. The early signs of anoxemia are excitability, stimulation, headache, rapid pulse and a dusky appearance of the nails.

Juvenile Diabetes. The treatment of children afflicted with diabetes offers today the most encouraging phase of the whole

problem. When we stop to think that before the insulin era they were doomed, that there was nothing to look forward to, that the physician had absolutely nothing to offer to the mother of such a child except a slow, gradual starvation of her child and finally, inevitable death; this was enough to shake even an old medical warrior. Joslin in his health talk on Diabetes (which by the way is a splendid little book for every physician to have in his waiting room because of the general information which it offers to the layman), makes this statement: "One of the most noted child specialists in the United States wished he might never have another diabetic child to treat, so sad was it to see a child starve to death." In those years, it was really a blessing if an intercurrent infection swept the child off of the list of the living, thus cutting short the prolonged agony of the child as well as of the parents.

We have had insulin only a decade, but what a difference do we see with these little diabetics. No longer do we deal with an undernourished, starving, fretful child, but with a vigorous youth growing up normally, full of mischief, full of ambition. Last summer while operating a summer camp for diabetic children it was really stimulating to me to see the trend of their conversation, which concerned going to college and speaking of professional occupations. And this was not just empty childish talk, for they actually are doing it. Just now four of my youthful diabetics whom I have had under my care for a number of years, are in college. And it is pleasing that their records show that they rank high scholastically.

Some time ago while addressing a group of Jewish women on the diabetic child, I said the following: "A diabetic child lives at a sacrifice, for only thus is his survival possible. He lives by self-imposed discipline. Don't think for a minute that when this child grows up, he will be an ordinary person. He will be the outstanding person in his group, for he has learned early in life what the other fellow learns late in life, if ever. Already some of these youthful diabetics, whose survival has been made possible, thanks to insulin, have shown their worth and are occupying places of responsibility and places of leadership in our social structure. Help these children now when they need your help most, watch their progress, for you will hear from them later."

And already we are hearing from them from all directions. They are growing up into serious-minded and responsible citizens. Each year there are more and more of them, so it behooves us to think of this rapidly growing group and to plan for them in our medical world. Summer camps for diabetic children are needed all over the country in order to give them an outdoor vacation during the

summer under proper conditions, such as have been provided for all other groups of children. When confronted about a camp by such a diabetic child, we can't say simply, "I never thought of it"— for he has, and he has a right to think of it. The psychologic influence of camp life on the diabetic child is most interesting. Many diabetic children come there with a sort of inferiority complex. This, however, is soon discarded after a few days at camp, and the child gains self-confidence and independence; it is a real joy to see such transformation taking place in these children. One can't help but feel that any sacrifice for them is worth while, and then, last, but not least, is to be considered the respite which a sojourn at camp offers to the mothers who are tied down by diabetic children 365 days of the year. It was really the thought of the mothers of these diabetic children which led me to the idea of such a camp years ago. I saw them bending under the great load, disheartened and exhausted. I felt then that the problem of such a diabetic child did not consist in the mere scientific management of that child, but in some consideration of the mother who carried the brunt of the load. It was the mother who had to be relieved, somehow, because her survival was essential for the survival of her child, and a summer camp for diabetic children is the answer both for the child and for the mother.

Pregnancy in Diabetes. Three of my diabetic girls already have grown up and have married and now have healthy babies of their own. That, too, was an impossibility in the past. In the first place, diabetic girls did not survive. Diabetic women in the preinsulin era had no menses and therefore were sterile. Pregnancies occurred but rarely and I believe that the few instances happened in mild cases of diabetes. Now, this whole picture has changed: a woman is again restored to her normal physiological plateau, even though she had not menstruated for 15 years before the insulin era. The mortality of diabetic mothers in the preinsulin era was high as one can see from Table 4. During the two years following parturi-

TABLE 4

Mortality of Diabetic Mothers in the Preinsulin Era

Author	Year	Per Cent Mortality
Hirschfeld	....	50
Williams	1926	27 — 23% more died in 2 years.
Hansen	1928	17
Colorni	....	46 — In the first two years.
Wiener	1923	30 — 21% more in 2½ years.

tion there was an added mortality of about 20 per cent. Therefore, it was a most serious procedure for a diabetic woman to attempt to go through pregnancy, for the risk was extreme. This state of affairs exists no longer for now these prospective mothers can be carried with safety through pregnancy and parturition.

It is a known fact that the babies of diabetic mothers are large, or, at any rate, many large babies are reported in the literature. Hence, an obstetrician never fails to investigate the possibility of the presence of diabetes in a mother who has given birth to a large baby. In the records which I gathered from the literature in a series of 54 babies born of diabetic mothers, the average weight was 10.1 pounds (the highest being 16 pounds) whereas the average weight of a child born of a normal mother, according to Williams is 7.25 pounds. This makes a ratio of 100:71. There are a few cases on record of babies born with diabetes, though this is of rare occurrence.

During the last few months of pregnancy the mother's diabetes improves and then it is necessary to lower the dosage of insulin. This very likely is due to the interdependent metabolism, with the fetus supplying insulin to the mother. This point has been questioned, but more and more evidence is being gathered for such an explanation. Another explanation is that the hyperglycemia of the mother stimulates the growth of the fetal insulogenic apparatus, which hypertrophies, or, at any rate, overfunctions and produces an excess of insulin. This in turn, reduces the amount of the mother's blood sugar and produces a large fetus. Perhaps both mechanism are at work. Theoretically it would seem dangerous for the fetus to develop a hyperfunctioning insulogenic apparatus; for then after birth cuts off the excessive intake of sugar due to the maternal hyperglycemia, such an overproduction of insulin would produce hypoglycemia in the child which might even be fatal. This will have to be worked out by obstetricians who have access to the data in a large number of cases; they might thus ascertain whether the death of such babies shortly after birth is due to hypoglycemic shock. This would seem probable.

SUMMARY

The classical symptoms of diabetes usually are lacking. Hence it is important to determine the amount of sugar in the blood as part of the general physical examination. Early recognition and early treatment are of extreme importance to the patient with diabetes.

The prevention of obesity is of prime importance in the prevention of diabetes. The effect of infections, both acute and chronic,

is discussed, and the importance of removing all foci of infection in diabetics is urged. In this connection, the constantly decreasing surgical mortality in diabetes is emphasized.

The treatment of children with diabetes presents a great challenge and inspiration to the physician, and this is a field of diabetes in which further progress may be anticipated. The course of diabetic mothers during pregnancy is discussed briefly.

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A CASE OF MEDIASTINAL DERMOID CYST CONTAINING PANCREATIC TISSUE, SIMULATING INTRA-THORACIC GOITER

Edward H. Crosby, M.D., and Allen Graham, M.D.

The mere addition of another case of mediastinal dermoid cyst to those already recorded in the literature would hardly seem to be justified. Our purpose in reporting the following case is to emphasize the possibility of the confusion of mediastinal dermoid cyst with intrathroacic goiter, and more particularly to record the occurrence, unique in this case so far as we have been able to determine, of pancreatic glandular and islet tissue in the cyst wall.

Case Report

A woman, 35 years of age, entered the Cleveland Clinic Hospital on October 22, 1929, complaining of marked dyspnea on exertion and a tumor in the suprasternal notch.

The tumor, which was first noticed two years previously as a slight, tender swelling, had persisted for two days and then disappeared. At that time the radiographic examination of the teeth gave negative findings; the tonsils were removed on account of chronic infection. Since its first appearance the swelling had recurred intermittently in the suprasternal notch and above the sternal end of the right clavicle, remaining for a few days and then subsiding.

At the time of admission the patient complained of shortness of breath, difficulty in swallowing, a slight non-productive cough and hoarseness of the voice. There had been no increased nervousness, no loss of appetite or weight and no gastrointestinal or genitourinary symptoms. The patient was well developed and was not acutely ill. The past and family history revealed nothing of importance.

Physical examination showed a tumor mass about the size of a hen's egg protruding into the suprasternal notch. During the act of swallowing this mass followed the movement of the trachea. There was no thrill, bruit or pulsation. An area of upper mediastinal dullness extended 4 cm. to the right and 5 cm. to the left of the midsternal line. Examination of the heart, lungs, abdomen and extremities revealed no significant abnormality.

Laboratory Findings. A roentgenogram of the chest (Fig. 1) revealed a large tumor mass in the upper mediastinum which was interpreted as a substernal goiter extending down to the third interspace anteriorly. The red blood cells numbered 4,000,000; white blood cells, 9,200; hemoglobin, 75 per cent. The basal metabolic rate was minus 7 per cent. The blood sugar before operation was 108 mg. per hundred cubic centimeters, one and one-half hours postprandial. The blood sugar after operation was 75 mg. per hundred cubic centimeters fasting. The Wassermann and Kahn reactions were negative. The urine was essentially negative on four examinations.
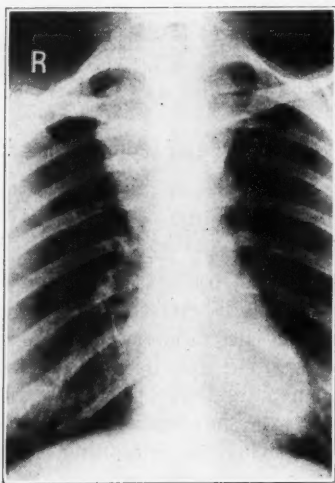

Fig. 1. Roentgenogram of the chest showing the mediastinal tumor.

A clinical diagnosis of substernal goiter was made and the patient was operated upon by Dr. G. W. Crile. Under nitrous oxide-oxygen anesthesia and novocain infiltration, a low collar incision was made as for thyroidectomy. The pretracheal fascia and muscles were separated in the median line exposing an apparently normal thyroid gland. Below the isthmus of the thyroid and bulging into the suprasternal notch, could be seen a tumor mass which extended into the mediastinum and apparently had no connection with the thyroid. Early in the process of freeing the tumor, a cyst was ruptured and approximately 150 to 200 cc. of thin, brownish fluid escaped. The character of the fluid suggested that the lesion was a dermoid cyst. The partially collapsed cyst-

wall was removed with considerable difficulty, on account of its intimate relationship to surrounding mediastinal structures. After the removal of the cyst, a large cavity, measuring approximately 12.5 cm. vertically and 7.5 cm. transversely, remained, bounded below by the arch of the aorta, anteriorly by the sternum, on the right by the innominate artery and vena cava, and on the left by the carotid and subclavian vessels. Posteriorly, the cyst-wall was in relation to the trachea and bronchi. After the cyst had been removed, the cavity was rinsed with saline and lightly packed with vaselinized scriflavine gauze. The operative wound was left open in order to allow free drainage. The patient was in excellent condition at the completion of the operation.

The postoperative reaction was very slight, and on the second postoperative day the cervical wound was closed around a small rubber catheter. The wound healed satisfactorily and the patient was discharged on the eighteenth postoperative day. At the time of discharge, abductor paralysis of the right vocal cord was present.

One year following the operation, a letter from the patient stated that she was in excellent health, had no evidence of recurrence and no hoarseness of the voice.

Macroscopically, the tissue received in the laboratory consisted of a ruptured, collapsed cyst-wall, weighing 45 grams and measuring 12 x 6 x 1.5 cm. It was irregularly pear-shaped. The cyst-wall was fibrous and varied from 3 mm. to 15 mm. in thickness. The inner surface was rough, somewhat trabeculated and had numerous, small masses of yellowish-brown granular material adherent to the lining. There were numerous small out-pouchings in the wall and several small, round, pouched-out areas, suggestive of ulceration, but without plastic exudate. In several areas, irregular masses of yellowish tissue were present in the wall, limited chiefly to the inner half. No hairs and no cartilage or bone could be recognized grossly. The outer surface of the cyst consisted of irregular, shaggy, fibrofatty tissue on the posterior aspect and a comparatively smooth, shiny, membranous layer on the anterior aspect.

Microscopically, the inner lining of the cyst consisted largely of fibrous tissue devoid of epithelium, but in some areas, particularly the thicker portions of the cyst-wall, there were fragments of stratified squamous epithelium, without keratohyaline material or hair shafts. Beneath this, there were a few lobules of sebaceous glands. No coil glands were recognized. In other areas, the inner lining consisted of simple, columnar mucus-secreting epithelium, and beneath this there was a large mass of non-encapsulated, lobu-

Fig. 2. Section of the cyst wall showing the mass of lobulated pancreatic tissue; x 6.
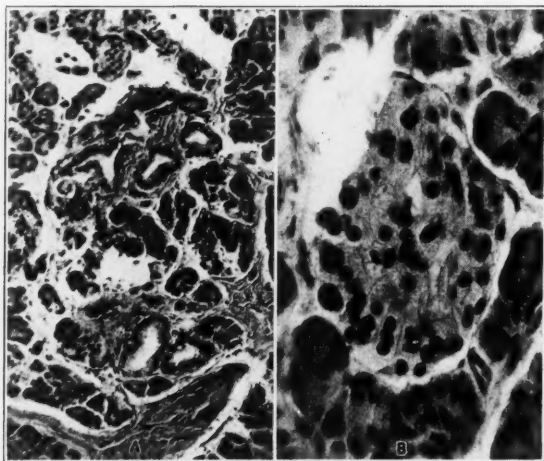

Fig. 3. (*a*) Pancreatic glandular tissue and ducts; x 150. (*b*) Pancreatic islet and glandular tissue; x 500.

lated, glandular tissue and ducts lined with cuboidal epithelium (Fig. 2). This tissue had the morphological characteristics of pancreas (Fig. 3). Scattered throughout this area were numerous small and large, solid masses of pale cells, morphologically similar to islet tissue. In other areas, the inner lining of the cyst was made up of stratified, columnar, ciliated epithelium, beneath which there were a few small, mucous glands in the stroma, suggestive of

pharyngeal mucosal structures. In this general neighborhood, there were several small islands of hyaline cartilage and fatty tissue in the cyst-wall, but no bone or dental structures were observed.

The middle zone of the cyst-wall consisted of collagenous, fibrous tissue showing extensive hyalinization and areas of mucoid degeneration. In numerous areas, there were irregular small and large collections of phagocytic cells containing yellowish-brown blood pigment and considerable lipoid material. A few scattered islands of perivascular lymphocytic infiltration were also found.

In the outer layers of the cyst-wall, several centimeters from the site of the pancreatic tissue, there were small masses of lobulated,
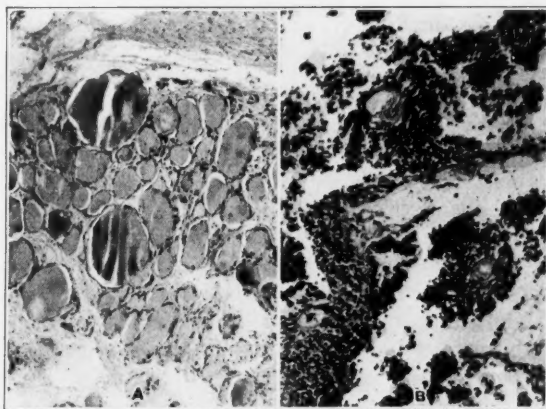

Fig. 4. From the outer layer of the cyst wall. (*a*) Thyroid tissue; x 100. (*b*) Thymic tissue; x 150.

colloid thyroid tissue (Fig 4), with vesicles lined by flattened epi-thelium, and considerable thymic tissue containing Hassall's corpuscles (Fig. 4). Some of the latter tissue extended well into the fibrous wall of the cyst and appeared to be somewhat compressed and atrophic. In such areas, Hassall's corpuscles were not present.

The most frequent location of intrathoracic dermoid cysts is the upper mediastinum. They are usually situated medially, but may extend laterally so that the major portion of the mass appears to the right or left of the midline. Generally, they are entirely within the thorax, but in about ten per cent of cases,[1] a swelling is apparent in the neck. The tumors vary greatly in size and consist of simple epidermoidal components or complex teratomatous growths. The symptoms are chiefly those due to mechanical ob-

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struction, compression or irritation of surrounding structures, and are dependent largely upon the size of the mass. The principal complication is infection, which may terminate in the formation of an abscess, with spontaneous rupture, mediastinitis, perforation of the trachea, emphysema, pneumonia or pulmonary abscess. Malignant neoplastic transformation occurs in about 15 per cent of cases.[2]

The literature concerning intrathoracic dermoid cysts has been reviewed by Kerr and Warfield,[1] Williams,[2] Hertzler,[3] Harris,[4] Hale,[5] and others. To these articles, the reader is referred for a complete bibliography.

Discussion

The case reported illustrates how easily a mediastinal dermoid cyst may be mistaken for an intrathoracic goiter. The comparatively rare occurrence of the former as contrasted with the frequent occurrence of the latter lesion is probably one of the reasons why the differentiation is not made clinically more frequently. In cases of intrathoracic goiter, it is usually possible to detect a direct continuity between the thyroid itself and the mediastinal swelling. On the other hand, in ninety per cent of the cases reviewed in the literature, the mediastinal dermoid cyst is not in continuity with the thyroid. Therefore, demonstration of this continuity, or the absence of continuity, may prove to be a useful sign in making the correct diagnosis, although up to the present time we have not had occasion to confirm this suggestion.

Misinterpretation of thyroidal and dermoidal lesions, at operation and on gross examination of the removed tissue in the laboratory, may occur also in another direction. A broken down, necrotic, cystic adenoma of the thyroid, whether cervical, partially or completely intrathoracic, may be mistaken for a dermoid cyst on account of the nature of the contents and the character of the cyst-wall. Such tumors generally are a part of the thyroid, and microscopical examination after their removal suffices to make the distinction.

In the title the tumor is stated to be a dermoid cyst. Its very complexity, however, probably necessitates its being classified as a teratomatous cyst. Derivatives of three germ layers are represented, namely, stratified squamous epithelium and sebaceous glands; ciliated columnar epithelium and pharyngeal mucous glands; thyroid and thymus; pancreas; fat and cartilage.

The branchial apparatus would seem to be the most probable source for the particular combination of tissues present in the

cyst-wall and the tumor may be looked upon as an inclusion cyst. In this sense, it is not exactly comparable to those ovarian dermoids, in which a totipotential germ cell is capable of differentiation in all of the tissues of the body.

The thyroid tissue in the cyst-wall in our case is probably of lateral branchial rather than of median pharyngeal origin. Its intimate association with thymic tissue would seem to warrant this conclusion. The occurrence of tissue having morphological character-istics identical with those of the pancreas is of interest and has not been reported heretofore as occurring in a mediastinal dermoid, as far as we know. The presence of this tissue as a pharyngeal deriva-tive is not so readily explained without invoking the theory of metaplasia. The salivary glands and the pancreas are physiological-ly related organs, but originate at widely separated points in the entodermal tract. If the primitive pharyngeal epithelium can dif-ferentiate into such diverse organs as the salivary glands, the thyroid and the thymus, it is not inconceivable that the pancreatic tissue in our case may likewise be of pharyngeal origin.

As was noted in the case report, no significant disturbance of sugar metabolism was detected.

SUMMARY

A case of dermoid cyst of the anterior mediastinum extending into the neck and simulating a substernal goiter is presented. The tumor was removed through a low collar incision as in thyroidec-tomy. Recovery was complete and the patient reported that she was in excellent health, one year following the operation.

The presence of histologically normal pancreatic tissue in the cyst-wall makes this case unique.

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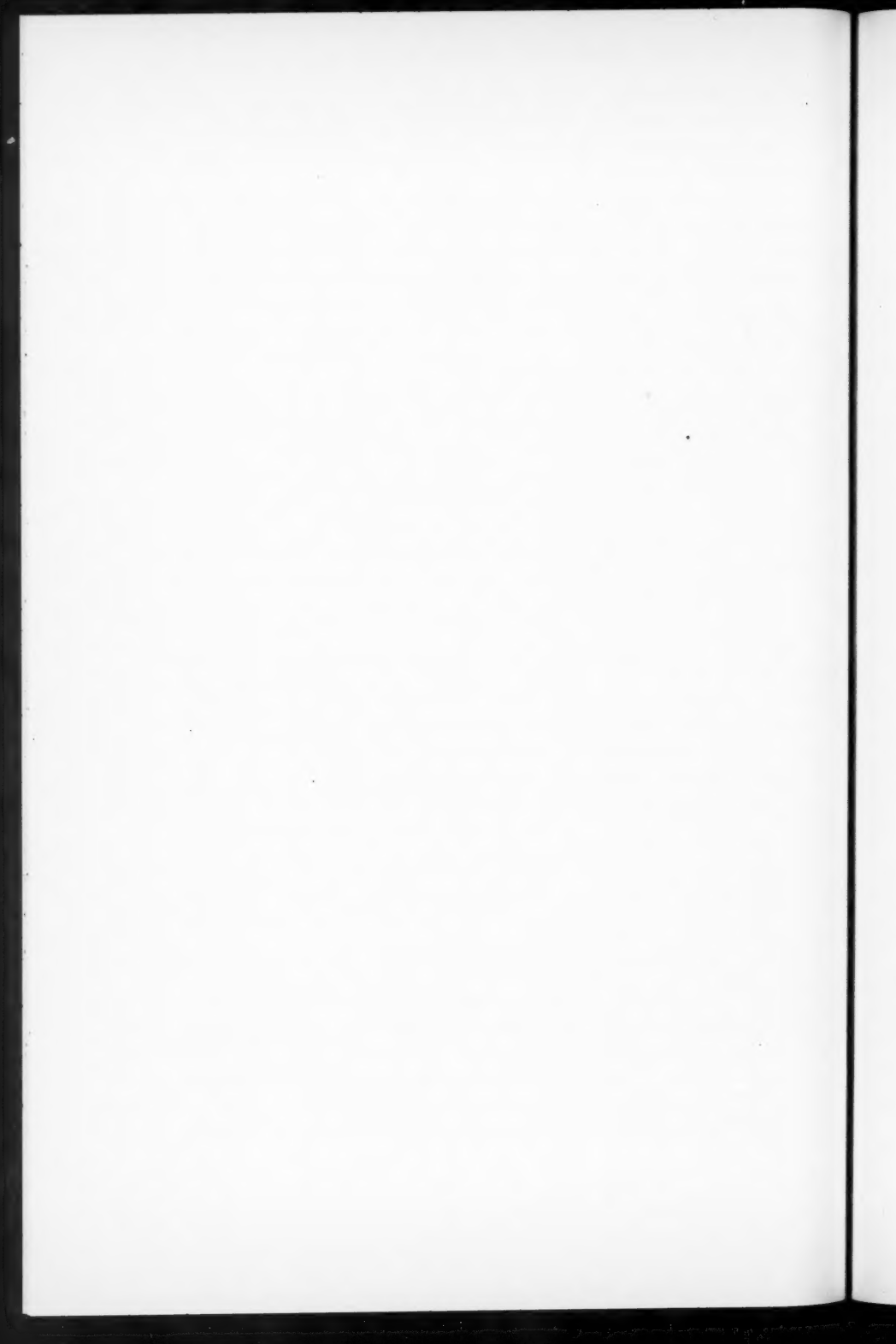
THE PHYSICAL FOUNDATION OF GRENZ-RAY THERAPY

Otto Glasser, Ph.D.

About six years ago, Dr. Gustav Bucky invited me to work with him on the investigation of the physical and clinical foundations of over-soft roentgen rays, which he had just introduced into practical use. We attempted to determine the wave lengths of the soft rays used by Dr. Bucky and to devise practical methods of measuring the quality and quantity of these rays, publishing the results in various papers, including those in the *American Journal of Roentgenology and Radium Therapy,*[1] and also in Dr. Bucky's book.[2]

Although considerable progress has been made in the past few years[3] in the clinical application of Grenz rays, the physical foundations have essentially remained the same. In the following presentation, therefore, some of the old data will necessarily be repeated and the few new developments will be added.

During the past few years, the name "Grenz," or border, rays has been used more and more in the literature to designate roentgen-ray beams of an average wave length of about 1.5 to 2.5 Angstroms, or of half value layers of 0.015 to 0.03 mm. of aluminum. Although from the biologic and clinical points of view the term "borderline rays" has its justification, it must be emphasized here that physically these rays form only a small part of the large spectrum of roentgen rays which has been known for many years.

Grenz-ray Apparatus

A Grenz-ray apparatus is shown in Fig. 1. The main transformer, the filament transformer, and the Grenz-ray tube are contained in a separate shock-proof box (*B*) which is suspended on a stand and can be easily adjusted. The tube acts as its own rectifier. The switchboard (*A*) contains the autotransformer and resistance control, a milliameter, a voltmeter, and also a water pump which forces water through the cooling device of the tube. One side of the transformer, usually that which supplies current to the water-cooled electrode, is grounded.

Well-known European types of Grenz-ray apparatus are manufactured by Siemens-Reiniger-Veifa, of Berlin; Sanitas, of Berlin; Koch and Sterzel, of Dresden; Seifert, of Hamburg, and Sommer, of
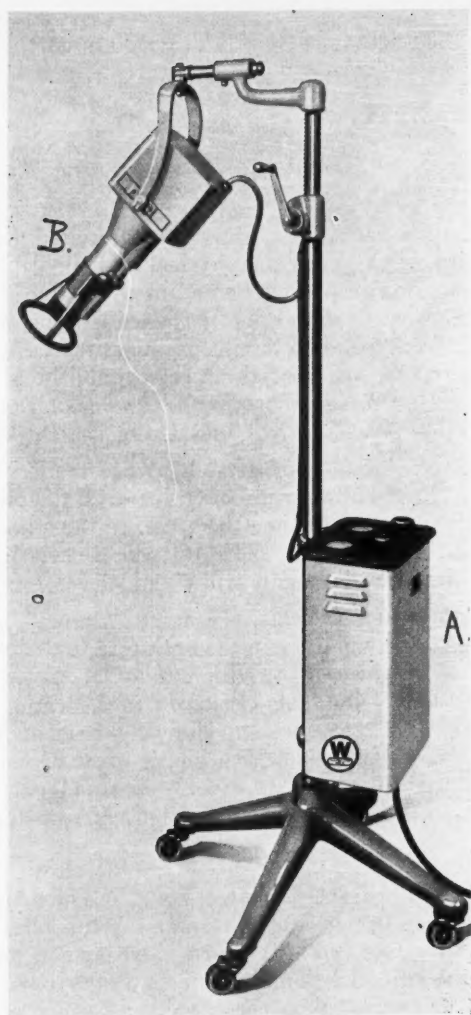
Fig. 1. Westinghouse Grenz-ray apparatus. (*A*) switchboard, (*B*) transformer and Grenz-ray tube.

Vienna. These types are all practically the same, that is, the control board, the transformer, and the tube are all mounted on one easily movable stand.
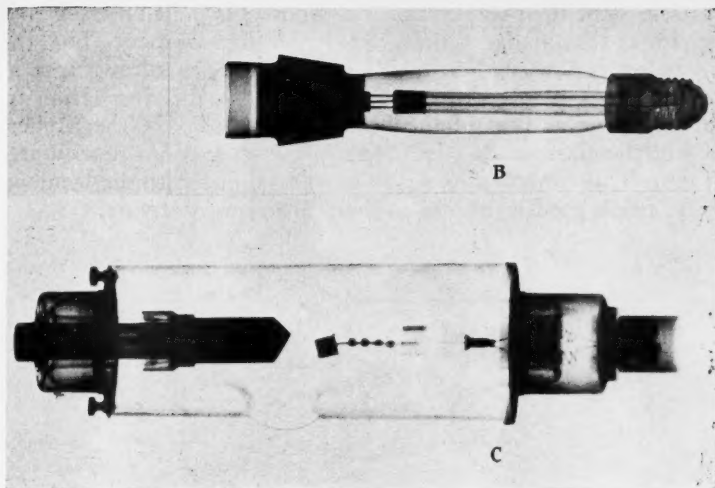
Fig. 2. (*B*) Muller Grenz-ray tube, (*C*) Siemens Grenz-ray tube.

GRENZ-RAY TUBES

In previous publications we described the commercial tubes (manufactured by C. H. F. Muller, of Hamburg, and by Simens-Reiniger-Veifa, of Berlin), which are still in use today (Fig. 2, B and C). We also described a tube made entirely of lithium glass, which was constructed in the laboratories of the Cleveland Clinic Foundation. At that time we called attention to the fact that this tube did not yet compare favorably with the commercial Grenz-ray tubes, since the transmission rate of the lithium glass used by us was less than that of the Lindemann glass used in the commercial tubes. We, therefore, abandoned the construction of lithium glass tubes and turned to another method in which we attempted to avoid the use of the Lindemann window. It must be remembered that the materials of which the Lindemann window is composed, namely, boron, beryllium, and lithium, are of low atomic weight and, therefore, easily permit the transmission of very soft rays. On the other hand, the Lindemann window must be rather thin (about 0.3 mm.) and, since it is slightly hygroscopic, it is not stable. Since it deteriorates in time unless it is carefully protected by a covering of lacquer, an attempt was made to obtain the same radiation transmission with a more stable window. Following the idea of the thin glass window used by Slack in his cathode-ray tube, we built a Grenz-ray tube with the same type of window.' The

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tube itself, with the exception of the window, is built on the same principles as that made by the C. H. F. Muller Company (Fig. 3). The window is a very thin bubble of glass which is drawn into a larger glass sphere. According to our tests, the filtering action is about the same as that of the Lindemann window of the Muller tube, but the glass window is more stable and does not deteriorate with time. This construction easily prevents damage to the window and also offers good resistance to the atmospheric pressure.
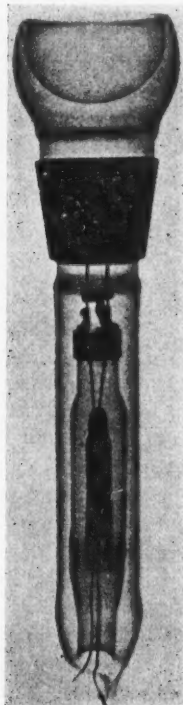
Fig. 3. Grenz-ray tube with Slack window.

Shortly after the construction of our tube and the publication of our article in *Strahlentherapie*, an advertisement of the Westinghouse X-ray Company appeared in the *Journal of the American Medical Association* (June 1931, XCVI, 7), describing a new Grenz-ray tube, built on the same principle as ours, on which scientists of the Westinghouse X-ray Company had been working independently for some time. This Westinghouse Grenz-ray tube (Fig. 4),
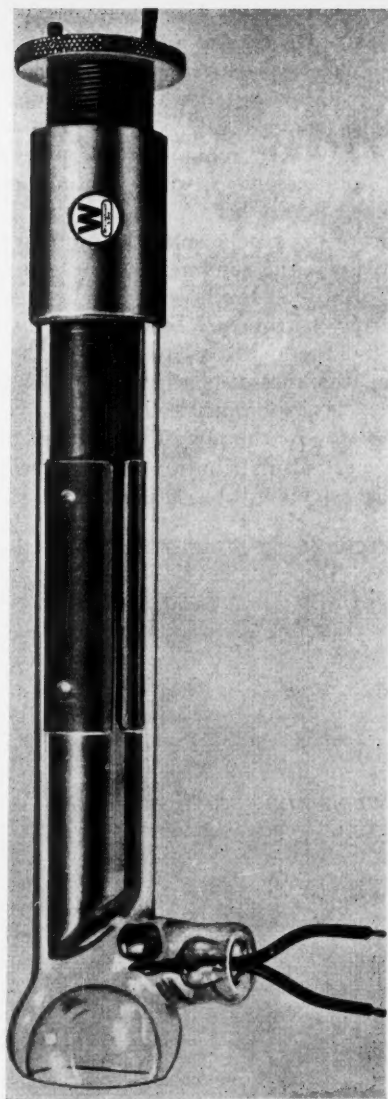
Fig. 4. Westinghouse Grenz-ray tube.

the Siemens, and the Muller tubes are the only commercial Grenz-ray tubes on the market at the present time.

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Spectrum of Grenz Rays

Grenz rays are roentgen rays of a wave length in the neighborhood of 2 A.U., which are produced by the special tubes just described. Because of the low potential used (around 10 K.V.), the spectrum is limited to about 1 A.U. at the short wave end. These short wave lengths have very characteristic properties, described in detail in earlier publications [1-8], which are important in therapy and must be discussed briefly here.

As Grenz rays are extremely soft, their quality and quantity depend very much upon the thickness of the glass or Lindemann glass window, and also upon the layer of air between the tube and the skin, or measuring instrument. The spectral distribution of the Grenz-ray beam, and therewith its quality, on the one hand, will change with various thicknesses of windows and with various focal skin distances; the relative intensities of Grenz-ray beams, on the other hand, will not follow the law of inverse squares of distance.

Curves of the spectral distribution of Grenz rays produced at various voltages as calculated by Kustner[9] are shown in Fig. 5.

Fig. 5. Spectrum of Grenz-ray beams produced at various voltages (Kustner).

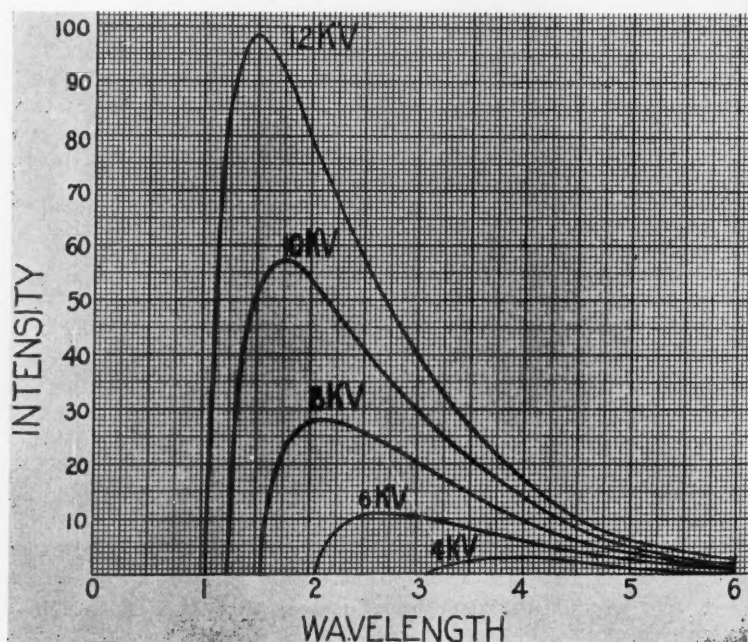Additional spectral distributions of Grenz-ray beams have been reported elsewhere.[1][2][3] It is interesting to study the spectral distribution as well as the rapid decrease in intensity for decreasing voltages. The absorption of Grenz rays in a Lindemann window and in air can be calculated for various wave lengths by means of the following formula[2]:

$$\mu \text{ air} = 0.00331\ \lambda^3 + 0.00022$$
$$\mu \text{ Lindemann} = 5.0\ \lambda^3 + 0.04$$

where μ is the coefficient of absorption and λ the wave length in Angstroms. These absorption coefficients permit the calculation of the absorption of the window and of air for various wave lengths.

TABLE I
Thickness of Lindemann windows in millimeters

K.V.	0.04	0.20	0.40
6	40.7	0.074	0.013
8	118.0	34.3	0.14
10	256.0	100.0	49.2

These data show the great influence of the thickness of the tube window and air layers upon the qualitative and quantitative distributions of the rays. It follows, therefore, that in order to obtain a correct estimate of the quality and quantity of Grenz rays at a given point, for instance, for the application of a certain dose, it is necessary that this determination be made at the point of the application of the rays. We shall, therefore, employ the half value layer in aluminum to indicate the radiation quality, and the number of roentgen units per minute to indicate the intensity of the radiation. In addition we shall specify the kilovoltage, the milliamperage, the tube, the target material, and the focal distance.

DETERMINATION OF QUALITY OF GRENZ RAYS

(*A*) *Indirect Method.* As we have just stated, it is advisable to supplement the direct method of determination of quality by the so-called indirect method, which consists in giving the secondary voltage and current and specifying the tube, target material, and focal skin distance used. The switchboards of all types of Grenz-ray apparatus mentioned above are equipped with a kilovolt meter, that is, a voltmeter which is connected across the primary of the transformer. The voltmeters are calibrated in kilovolts in the factory by various methods. Whenever feasible, it is advisable to recalibrate these meters from time to time by means of sphere gaps or spark gaps. Better than sphere gaps are electrostatic voltmeters which are reliable and can be easily procured for the voltages
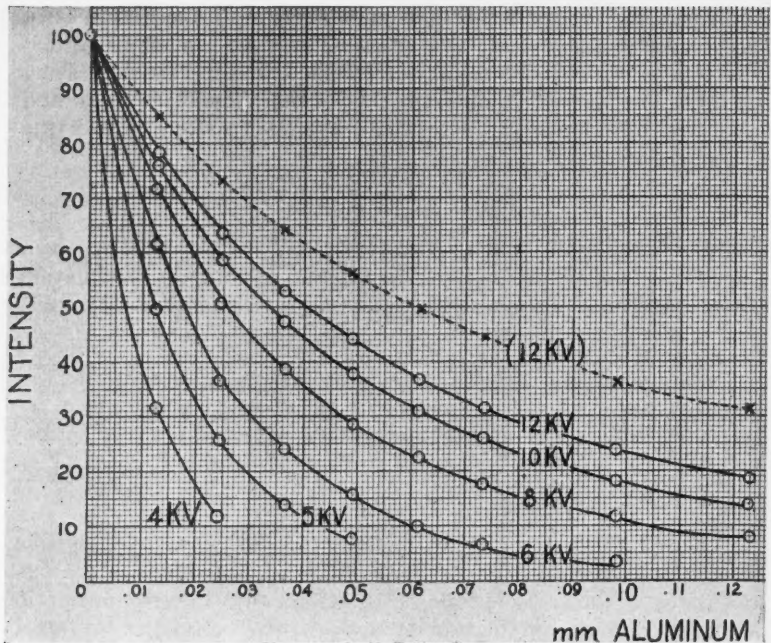
Fig. 6. Absorption curves for Grenz rays produced at various voltages.

used in Grenz-ray therapy. It is not sufficient, however, to connect the gap right across the terminals of the Grenz-ray tube since in practically all Grenz-ray apparatus the negative phase of the current is not suppressed. This negative phase usually is higher than that which reaches the tube and must, therefore, be excluded by means of a valve tube which must be included in the secondary circuit connected in series with the sphere gap. In order to avoid mistakes, secondary voltages should always be given in peak and not in effective voltages. The secondary current is read on a milliamperemeter which is also mounted on the switchboard of the Grenz-ray apparatus.

(B) *Direct Method*. In addition to the data described in the preceding paragraphs it is advisable to indicate the radiation quality by direct means. A number of years ago we suggested the use of the half value layer in aluminum to specify radiation quality in Grenz-ray therapy. This half value layer can be determined satisfactorily by means of the ionization dosimeter which will be described later. In our measurements we used pure aluminum foil of

0.0125 mm. thickness as an absorbent material. Cellophane, as well as other substances, has been suggested for this purpose. We found, however, that aluminum was superior to other materials since it can be obtained in uniform thickness and does not show the variations in absorption due to impurities or irregularities in composition inherent in most other materials. Furthermore, some of the other materials are hygroscopic and, therefore, change with time.

Complete absorption curves on Grenz rays produced at various voltages have been described,[1][2] and the more important data are again reproduced (Fig. 6). The various intensities were measured with a specially constructed ionization chamber, made of goldbeater's skin and having a volume of 1 cubic centimeter. This chamber measures the radiation intensity independently of the wave lengths over the range used in Grenz-ray therapy. The curves were obtained with a Muller tube, the distance from the window to the chamber being 4 cm., that is, 9.6 cm. from the focus to the chamber. For the sake of comparison, in addition to the curves obtained with the Muller Grenz-ray tube at 4, 5, 6, 8, 10, and 12 K.V., an absorption curve is illustrated which is obtained by means of an ordinary Coolidge tube operated at 12 kilovolts. As we have stated, these curves hold only for the special tubes with which they have been measured; they may be quite different for other tubes. Furthermore, the quality distribution measured would be different if the measurements had been made at greater distances since the air would act as a filter and "harden" the Grenz-ray beams. We have previously discussed this effect and further extensive experimental data regarding it were recently presented by Meyer,[10] using filters of 0.01, 0.013, 0.018, 0.025, 0.031, and 0.035 mm. aluminum and a Siemens integral dosimeter with a Grenz-ray chamber. This author also called attention to the fact noticed by others[1][2][11] that, due to the filtering effect of the sputtered tungsten on the window of the tube, Grenz-ray tubes harden with use. For this reason, it is necessary to repeat dosage measurements on Grenz-ray tubes at least after every 100 hours of use.

It must be mentioned here that some authors believe that the half value layer method of indicating radiation quality for Grenz rays is not necessary, and that indirect factors indicating the quality are entirely sufficient. However, on this point opinions are divided and controversies have arisen.[12]

Berger,[13] who at first was against the use of the half value layer, has since constructed a practical little apparatus to measure it. The apparatus consists of an aluminum foil of 0.01 mm. thickness which can be rotated around its axis in a small cylinder, the latter

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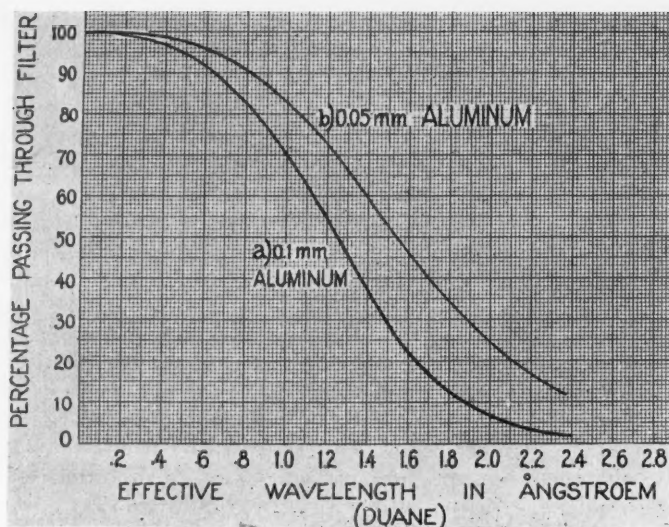
Fig. 7. Curves for the determination of the effective wave length for Grenz rays (Duane).

being placed between the Grenz-ray tube and the ionization chamber. The Grenz rays, which first pass through a small diaphragm, must penetrate different thicknesses of aluminum foil, depending upon the angle between the foil and the path of the rays. A pointer connected to the foil permits the reading of the angle on the outside of the apparatus on a scale which is directly calibrated in respective thicknesses. In our opinion, the determination of the half value layer is indispensable in Grenz-ray therapy.

Another method of indicating radiation quality is the effective wave length method suggested by Duane.'' This has also been discussed previously and various data have been reported' ' on the effective wave lengths of Grenz-ray beams Fig. 7). We shall therefore, not go into this question again, especially since, in 1931, the International Standardization Committee at the Third International Congress of Radiology suggested that the roentgen-ray beams be characterized by the half value layer.

Absorption of Grenz Rays in the Human Skin

Formerly we presented half value layers for various layers of the human skin in combination with the half value layer in water and aluminum. The most important data in this connection are
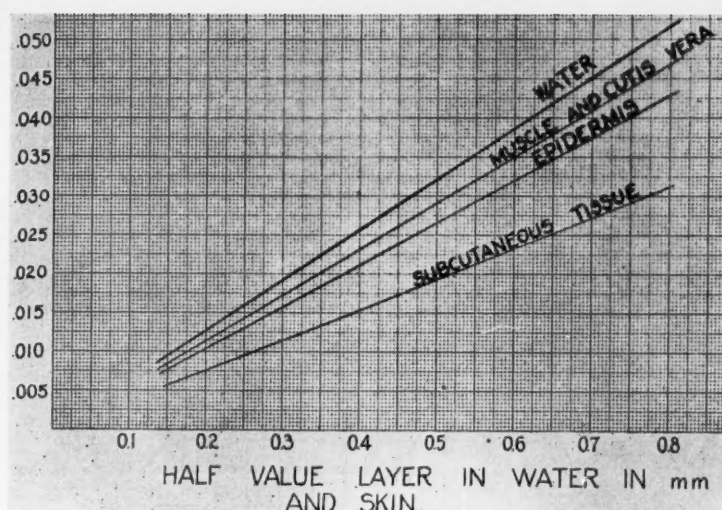
Fig. 8. Half value layer in aluminum as opposed to half value layer in water and various parts of the skin.

TABLE II

Half Value Layer in Aluminum as Compared with Half Value Layers in Water, Muscle, Cutis Vera, Epidermis, and Subcutaneous Tissue (in Millimeters)

Aluminum	Water	Muscle, cutis vera	Epidermis	Subsutaneous tissue
0.007	0.12	0.13	0.14	0.20
0.0125	0.20	0.22	0.24	0.33
0.0175	0.28	0.31	0.34	0.46
0.0250	0.39	0.43	0.47	0.64
0.0335	0.52	0.57	0.62	0.86
0.0400	0.62	0.68	0.74	1.02

contained in Table II, which gives an idea as to how far the Grenz rays of various half value layers penetrate into the skin (Fig. 8).

It is interesting to compare the absorption of the Grenz rays in skin with that of roentgen rays usually employed in dermatology. Only a very low percentage of roentgen rays produced at about 100 K.V. are absorbed by 1 mm. of skin, while over 50 per cent of Grenz rays produced at 10 K.V. are absorbed by 1 mm. of skin. This is illustrated in Fig. 9, taken from Bucky's book.[2]

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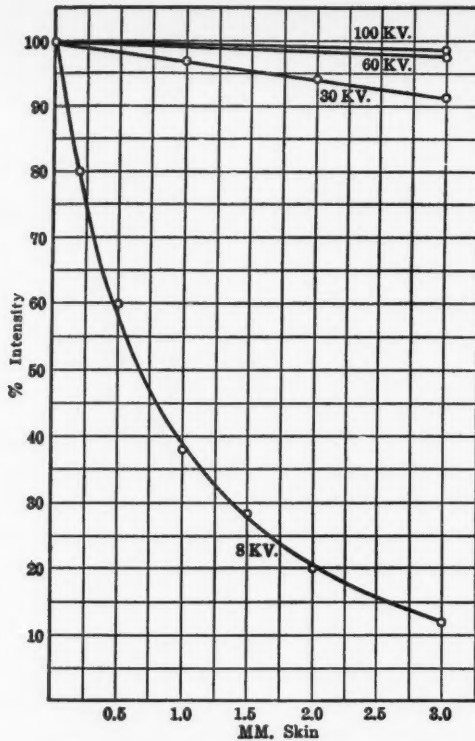
Fig. 9. Comparison of the absorption of Grenz rays and harder roentgen rays in the skin.

DETERMINATION OF THE QUANTITY OF GRENZ RAYS

(*A*) *Indirect Method*. The indirect method of measuring the quantity of Grenz rays by means of the milliamperemeter has been found to be unsatisfactory. The intensity delivered by various tubes for the same number of milliamperes varies widely. The Grenz-ray apparatus also must be calibrated at various voltages for various milliamperages, since the secondary current changes if the voltage is changed. It is, therefore, advisable always to use the same milliamperage for a given voltage. It is still better, how-ever, to measure the quantity of radiation by the direct method at the point of application.

(*B*) *Direct Method*. The quantity of Grenz rays is best de-termined by, and expressed in, the international roentgen unit,
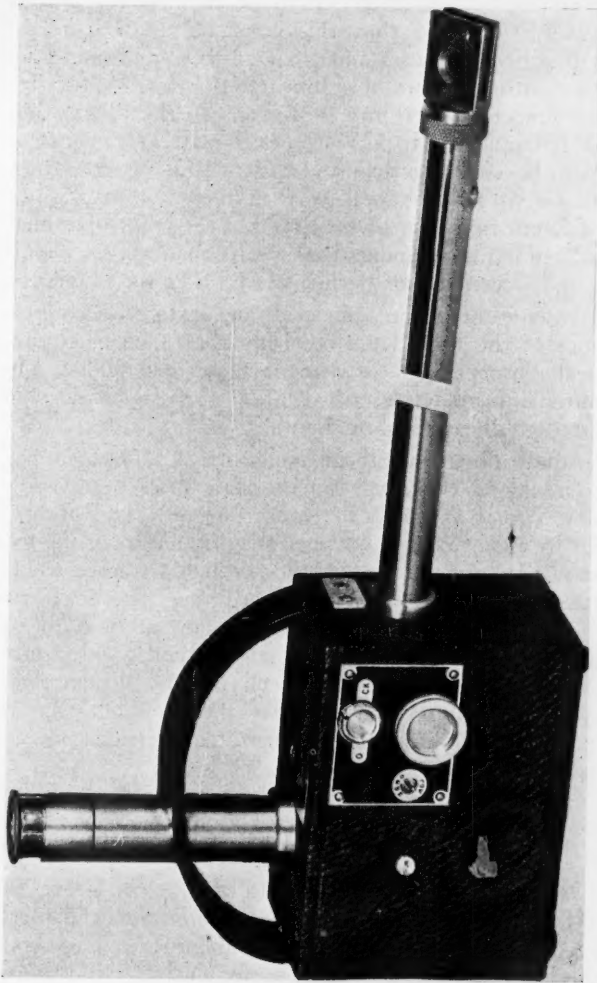
Fig. 10. Victoreen r meter with Grenz-ray chamber.

the definition of which, as well as the methods of determination, has been described frequently. A few years ago we modified our apparatus for the determination of the r unit in order to use it for the soft Grenz rays.' Since that time we have calibrated in roentgen units specially constructed dosimeters with small ionization chambers and our calibration compares favorably with that of others.

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Originally we used 1 c.c. chambers built entirely of goldbeater's skin. However, we found that this construction was not stable enough for practical purposes and changed to a small metal ionization chamber with windows of goldbeater's skin (Fig. 10). It may be used in connection with any dosimeter; in the illustration, for instance, it is connected to a Victoreen r meter. This instrument has proven to be very practical and satisfactory for dose measurements with Grenz rays as well as with roentgen rays, since the intensity of Grenz rays may be measured at the point of application of the rays.* Similar instruments have been constructed by Kustner, in Gottingen, by Siemens, in Berlin, and by Strauss, in Vienna.

Since it was found to be sufficiently accurate on account of its independence of the wave lengths within the range of Grenz rays employed, all absorption measurements described above, and the dose measurements to be described later, were made by means of our calibrated goldbeater's skin chamber.

Photographic films have been suggested for dosage measurements in Grenz-ray therapy,[15] but the difficulties involved would seem to be too great to permit of accurate results. This observation is borne out by a controversy between the originators of the method and Reisner.[16] Another dosage method which we have used with good success is the photometer.[17] Packard[18] uses the death rate of *Drosophila* eggs to measure biologically the intensity of Grenz rays. Thaller[19] recently suggested a new method making use of a specially constructed photo-electric cell for the measurement of Grenz rays. In making these intensity measurements on Muller Grenz-ray tubes which have a ring-shaped focus, special precautions must be taken in order to avoid errors.[20]

Dose Measurements on Grenz Rays in Practical Use

In his latest papers, Bucky suggests the use of Grenz rays of half value layers of 0.015 to 0.03 mm. of aluminum and focal skin distances from 6 to 15 centimeters. In Table III we have collected a series of data on Grenz-ray qualities for various conditions from which it will be seen that the qualities suggested by Bucky were produced with our tubes at voltages of from 6 to 10 kilovolts.

Fig. 11 shows more data on Grenz-ray intensities for various focal distances and various voltages as published recently.[19] The data show that the intensity decreases rapidly with decreasing kilovoltage and increasing distances. We have stated previously[13] that it is difficult to fix erythema doses for Grenz rays and have

*Courtesy of the Victoreen Instrument Company, Cleveland, Ohio.

TABLE III

Half Value Layer in Millimeter Aluminum for Grenz Rays, Muller Tube, Chromium Iron Target, 10 Milliamperes

K.V.	4 cm. distance (window chamber), millimeter	20 cm. distance (window chamber), millimeter
4	0.007	. . . . .
5	0.0125	. . . . .
6	0.0175	0.0195
8	0.0250	0.0315
10	0.0335	0.0435
12	0.0400	0.0610

In Table IV are presented various Grenz-ray intensities in roentgen units.

TABLE IV

Radiation Intensities in R/Min. and Erythema Times per Dose of 250 r for Different Distances. Muller Tube, 10 Milliamperes

Distance in cm. (window chamber)	6 K.V. radiation		10 K.V. radiation	
	r/min.	Erythema time in minutes for 250 r	r/min.	Erythema time in minutes for 250 r
4	47.2	5.3	396.0	0.6
6	27.6	9.0	239.0	1.0
8	18.2	13.7	162.0	1.5
10	12.7	19.7	126.0	2.0
15	5.9	42.3	66.5	3.8
20	3.2	78.0	42.5	5.9

Radiation Intensities and Erythema Times per Dose of 250 r for Different Potentials. Muller Tube, 10 Milliamperes

E.m.f., K.V.	20 centimeters distance window chamber		4 centimeters distance window chamber	
	r/min.	Erythema time in minutes for 250 r	r/min.	Erythema time in minutes for 250 r
5	0.54	463.0	10.5	23.8
6	3.2	78.0	47.2	5.3
8	16.8	14.9	195.0	1.3
10	42.5	5.9	396.0	0.6
12	98.5	2.5	710.0	0.35

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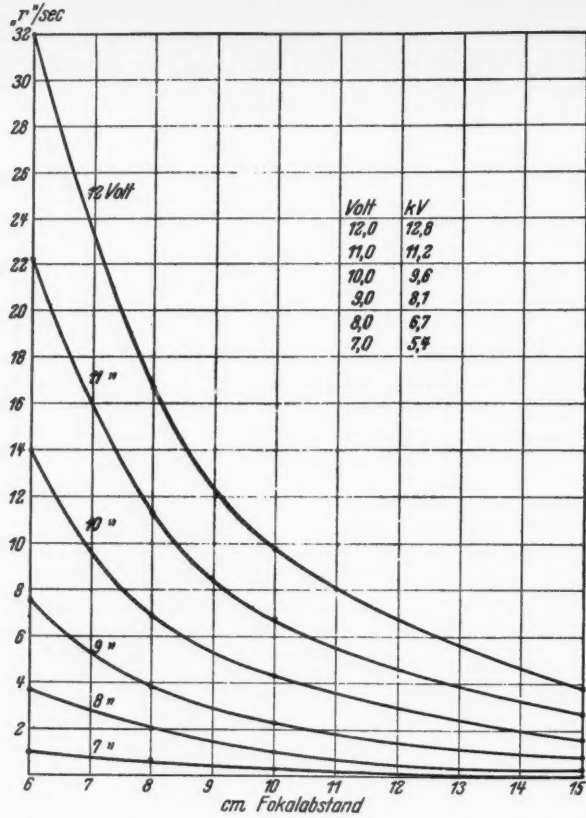
Fig. 11. Intensity of Grenz-ray beams produced at various voltages for various focal skin distances (Meyer).

made the suggestion that the value of 250 r units be accepted as a threshold erythema dose. Further experiments have shown that this value is approximately correct. Hausser and Schlecter[21] presented data on measurements of erythema doses with Grenz rays as compared to erythema doses produced with roentgen rays and have shown that the increase in the biologic reaction with increasing doses is much slower for Grenz rays than for X-rays (Fig. 12). Finally, attention must be called to the difficulty in radiating larger skin areas with the ordinary type tube, since at 4 cm. distance the diameter of the irradiated area is only about 4 centimeters, and there is a marked decrease in intensity in this area from the
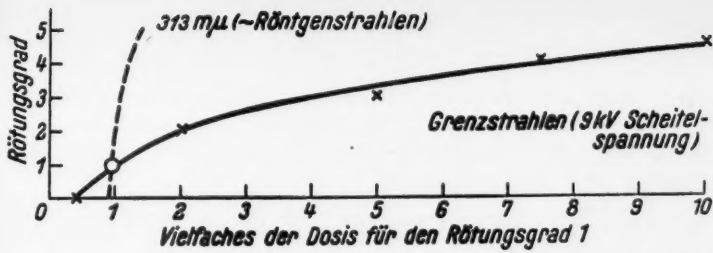
Fig. 12. Comparison of the degree of redness of the skin after application of increasing doses of roentgen rays and of Grenz rays (Hausser and Schlechter). Rotungsgrad: degree of erythema. Vielfaches der Dosis fur den Rotungsgrad I: multiple of the dose to produce one degree of erythema.

center toward the periphery. For practical treatments careful planning" of the combination of various areas has to precede the treatment: for a typical case this is illustrated in Fig. 13.
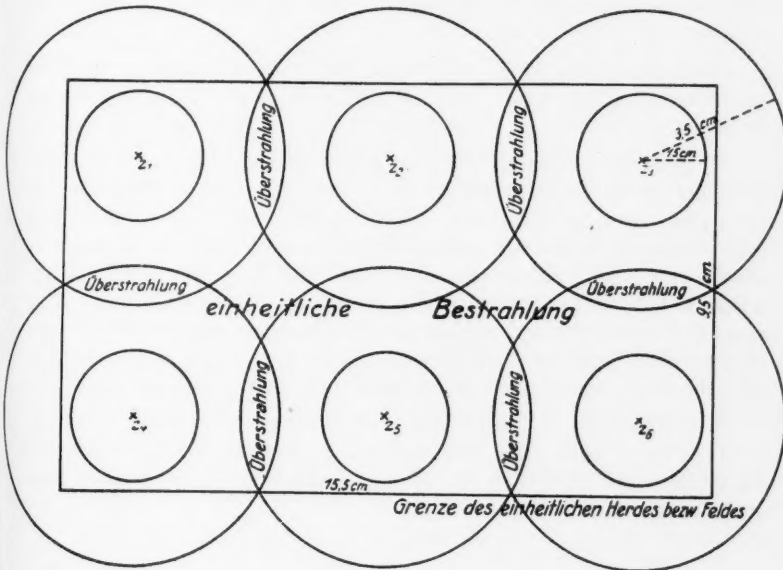
Fig. 13. Mapping out a large area of irradiation by combining various Grenz-ray beams.

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Summary

Grenz rays are soft roentgen rays having a wave length of from 1 to 3 Angstrom units. They are produced in tubes with Lindemann glass or specially constructed windows of ordinary glass with voltages of from 6 to 10 kilovolts.

High tension apparatus and tubes for the production of Grenz rays are described.

Grenz rays are so soft that they are absorbed in the window of the tube and air to a considerable degree, therefore, only direct determinations of the radiation quality and quantity at the site of application are found to be satisfactory. These data should be accompanied preferably by an indication of the kilovoltage, the milliamperage, the type of tube, the target material, and the focal skin distance.

The absorption of Grenz rays in aluminum foil of 0.125 mm. thickness has been determined for different conditions of radiation and the half value layers of this radiation are found to be between 0.04 and 0.01 mm. of aluminum.

Data for translating half value layers of aluminum into half value layers of air, water, muscle, and various parts of the skin are given.

A small ionization chamber of goldbeater's skin, which is practical for dosage measurements in Grenz rays and is calibrated in roentgen units, is described. This chamber may be connected to any ionization dosimeter and the radiation intensity of Grenz rays may be measured independently of the wave lengths over the range used in Grenz-ray therapy. By means of this goldbeater's skin chamber the intensity of Grenz rays has been measured in r per minute for a number of radiation conditions, having been found to vary between about 400 r per minute and 0.5 r per minute.

The threshold erythema dose for Grenz rays is in the neighborhood of 250 r units. The increase of the physiologic effect of Grenz rays upon the skin with increasing dosages is much smaller than it is for roentgen rays.

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SUBUNGUAL MELANOMA IN NEGROES

James A. Dickson, M.D., and T. F. Jarman, M.D.

Melanotic tumors of all types are very rare in the Negro. Adair, Pack, and Nicholson[1] in a review of the literature on this subject found fourteen reported cases up to 1926. One of three cases of subungual melanoma which these authors observed at Memorial Hospital occurred in a Negro. In 1927 Bauer[2] reported two cases of melanotic tumors occurring in Negroes, one of which was a subungual melanoma. We can now add a further case to those already reported.

Fig. 1. Photograph of fifth finger of left hand, showing subungual melanoma.

A Negress, seventy-three years of age, came to the Cleveland Clinic complaining of discoloration of the fifth finger of the left hand. The following history was obtained: For twenty years she had had a "black spot" on the nail of the fifth finger of the left hand. This spot grew gradually larger and another developed, so that there were two large discolored areas on the nail, both quite black in color. This condition had remained constant for the past fifteen years, during which time the area of discoloration had not increased in size. Six months previous to the admission of the patient, the nail split, assuming a bifid character. Up to that time the nail had been normal in shape and configuration (Fig. 1).

Physical examination of the patient revealed nothing abnormal apart from the black discoloration of the fifth finger of the left hand, including the nail which was bifid due to a splitting down its centre as far as the nail bed. Pus could be evacuated from the central split
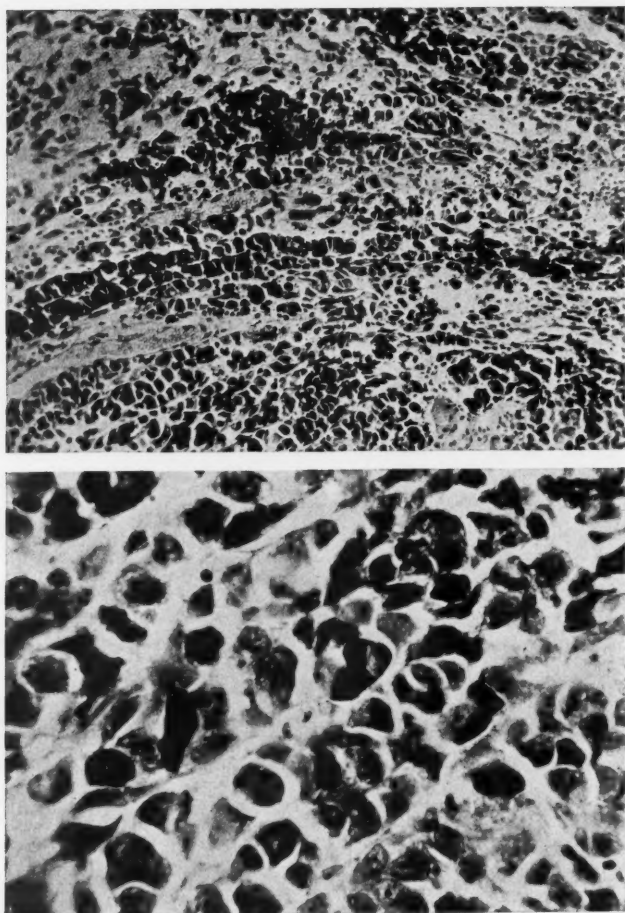
Fig. 2. (*A*) Photomicrograph of subungual melanoma (x 150). (*B*) High-power photomicrograph of same area of tissue as shown in *A* (x 600).

down the nail. The palmar aspect of the tip of the finger presented an area of dark, gangrenous-appearing skin. No enlarged regional lymph-nodes could be detected.

Clinically, the lesion was thought to be an infected, melanotic, pigmented tumor, the exact pathological nature of which could not be determined. Microscopical examination of a small piece of tissue from the nail bed showed that the tumor was a subungual melanoma of low-grade malignancy.

The finger was amputated at the metacarpo-phalangeal joint and the head of the metacarpal bone was removed. The wound healed by first intention.

The following is the report of the microscopical examination of the removed tissue:

"Section of tissue through the nail bed shows thickened epidermis covered by a heavy layer of keratohyaline material in the region of the base of the nail. In the region of the tip, the epithelium is destroyed, the tissue is ulcerated, and in the deeper layers there is a large quantity of very cellular tissue rich in melanin pigment. In some areas the quantity of melanin pigment is large and the number of actively growing tumor cells is small. This is particularly true of the area near the base of the nail. Near the tip of the finger the tumor cells predominate over the pigment. The vast majority of the cells, however, contain fine, granular, dark-brown pigment in the cytoplasm. The tumor cells are quite large; some are multinucleated. Mitotic figures are rare." (Fig. 2.)

Second Pathological Report. "Longitudinal section through the distal phalanx, including the nail, soft tissues and bone — which has been decalcified — shows keratosis of the nail bed and ulceration of the tip of the finger. Considerable diffuse inflammatory reaction is present in the soft tissues. There is no involvement of bone. A large amount of melanin pigment may be observed below the epidermis under the tip of the nail. The melanin-forming cells show very little evidence of active growth."

The pathological diagnosis was *subungual melanoma* of low-grade malignancy. The patient was instructed to return to the clinic at frequent intervals for examination but she neglected to do so. She was visited July 20, 1931, ten and a half months following the removal of the finger. The amputation scar was found to be in perfect condition and there was no evidence of any neoplastic process.

The left epitrochlear and axillary lymph glands, however, were definitely enlarged and hard, but not fixed. The patient was in excellent condition and had not noticed the presence of the nodules in the left epitrochlear and axillary regions.

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TRAUMATIC SUBDURAL HEMATOMA

WITH PARTICULAR REFERENCE TO THE LATENT INTERVAL

W. James Gardner, M.D.

Traumatic subdural hematoma is a definite clinical entity that has been given considerable attention in the medical literature since Virchow's classic description[1] of "hematomas of the dura mater" in 1857. The lesion consists of an encysted collection of blood, situated between the dura and the arachnoid membranes, usually over the convexity of the cerebral hemisphere. It is my aim to sketch briefly the clinical and pathologic aspects of this interesting lesion and to dwell particularly on the reason for its delayed clinical manifestations.

The majority of published reports of cases of traumatic subdural hematoma are similar in one respect, that is, in the occurrence of a latent interval between the reception of trauma and the onset of pressure symptoms. The cranial trauma that was responsible may have been severe or so trivial as to be readily forgotten. In many instances a history of trauma that had been denied previously has been obtained after operative verification of the lesion has led to closer questioning of the patient or his relatives. The latent interval may vary from a few hours to many months or even years, and during this period the symptoms may be slight or even entirely absent.

The onset of symptoms may be insidious or rapidly progressive. The most common symptom is headache, occasionally associated with vomiting. Mental disturbances occur more frequently in the presence of this condition than in the case of any other space-filling intracranial lesion. Inequality of the pupils, papilledema and pyramidal tract signs are frequently present. Convulsions, either jacksonian or generalized, may occur. However, lateralizing signs are not of great significance, since the lesion is often found on the side opposite to that which is indicated by the symptoms. In a certain percentage of cases the lesion is bilateral.

During the past few years, seven cases of traumatic subdural hematoma have been studied in the neurosurgical department of the Cleveland Clinic Hospital. Five of the patients recovered following an operation, while two died with the condition undiagnosed (Fig. 1). The following case is a fairly typical one.

Fig. 1. Postmortem specimen of bilateral subdural hematoma.

REPORT OF A CASE

History. A man, aged 52, was admitted to the Cleveland Clinic on Feb. 4, 1930, with lapse of memory as the chief complaint. On Dec. 12, 1929, he had driven his automobile into a ditch, colliding with a concrete culvert. He was unconscious for about an hour and a half. On regaining consciousness he did not recall events that had occurred for approximately ten minutes prior to the accident. He sustained a small laceration over the left eye. He remained at home for four weeks, during which time he did not feel himself; after this he resumed work as a certified public accountant, feeling that he was entirely well. Three weeks later, he had a period of complete amnesia lasting for forty-eight hours. For this reason he was referred to the clinic by Dr. Paul Zinkham, of Ravenna, Ohio.

Examination. The patient was alert mentally and apparently in good health; the temperature was normal, the pulse rate, 88, and the blood pressure, 126 systolic and 90 diastolic. The ocular fundi presented an early papilledema. Roentgen examination of the skull gave negative results for any evidence of fracture. Neurologic examination gave negative results. The spinal fluid pressure was 240 mm. of water. The fluid was clear and colorless and contained 2 cells. The Wassermann and colloidal gold reactions were negative.

Course. Forty-eight hours after admission, the patient lapsed into semistupor, and a complete paralysis of the left third nerve developed, with a slight weakness in drawing up the right corner of the mouth. The pulse rate was 48, and the blood pressure, 188 systolic and 144 diastolic. An immediate operation was decided on, the preoperative diagnosis being intracranial hemorrhage.

Operations. Since the symptoms indicated a lesion on the left side, the usual subtemporal decompression was performed on that side. Except for increased intracranial pressure, the observations at the operation were entirely negative. Forty-eight hours later, the patient's condition was still more alarming, and because the presence of a clot on the opposite side was suspected a right subtemporal decompression was performed. When the dura was incised, a large thin-walled cyst containing dark, semifluid blood was evacuated. The underlying cortex was entirely normal. No fresh bleeding followed the evacuation, and the would was closed without drainage. The patient made a complete uneventful recovery, and has remained well to date.

Summary. In this case a man sustained a cranial trauma resulting in mild symptoms for four weeks, followed by a symptom-free interval of three weeks. Seven weeks after the trauma, he had a three-day period of amnesia, and one week later passed into stupor. An encysted subdural hematoma was found on the side opposite to that indicated by the symptoms. This history differs in but few details from that in many cases reported in the literature.

CHARACTER OF THE LESION

The gross as well as the microscopic characteristics of these lesions are of interest. Grossly, the outer wall of the hemorrhagic cyst, which is next to the dura, is a great deal thicker than the inner wall, which is next to the arachnoid. The outer wall is adherent to, but strips easily from, the inner surface of the dura, leaving relatively few bleeding points. As a rule, the inner wall is not at all adherent to the arachnoid and is avascular. The contents of the cysts vary from a thin yellow or brown fluid containing shaggy remnants of degenerating clot to a firm currant-jelly clot.

The microscopic appearance of the neomembrane surrounding the degenerating clot has been well described by many authors, notably by Putnam and Cushing[2] in 1925. Briefly, the outer wall may be said to resemble a highly vascular layer of granulation tissue of varying thickness, slightly adherent to the inner surface of the dura. Putnam and Cushing were particularly impressed with the frequent occurrence of a layer of large irregular "mesothelial-lined

blood spaces" in the neomembrane just below the line of demarcation between the dura and the membrane. The inner wall of the cyst is much thinner, and consists of a layer of fibrous tissue, a few cells in thickness, with a single layer of mesothelium on the surface next to the arachnoid. This portion of the membrane is entirely avascular.

In cases of subdural hematoma it is seldom possible to demonstrate the original source of the hemorrhage. The preponderance of evidence, however, would seem to indicate that the vascular rupture occurs in one or more of the cerebral veins as they cross the subdural space to enter the longitudinal sinus.[1] Certainly this is the most likely source of subdural hemorrhage during the course of a cranial operation.

THE LATENT INTERVAL

With this introduction, consideration may be given to the latent interval between the occurrence of the trauma and the onset of symptoms of increased intracranial pressure. In analyzing a large series of case reports of traumatic subdural hematoma, it is difficult to escape the conviction that the lesion must undergo a progressive augmentation in size subsequent to its initial formation. Otherwise, why should a patient, apparently completely recovered from the effects of a cranial trauma, begin to show symptoms of increasing intracranial pressure some weeks or months later?

The most obvious explanation of the progressive enlargement of these lesions is that there occurs a slow, continuous or perhaps an intermittent bleeding from the responsible vessel.[1] Yet, nowhere else in the body does an injured blood vessel behave in this fashion. These lesions occur in persons of any age; vascular disease does not constitute an etiologic factor, and a hemorrhagic diathesis has never been demonstrated.

It has been suggested[1] that the granulation tissue that constitutes the outer wall of the hematoma may be the seat of repeated hemorrhages, either from a capillary source or from the large "mesothelial-lined blood spaces," which appear to communicate with the capillaries. Arguments against this hypothesis are that spontaneous hemorrhage does not occur from newly formed blood vessels elsewhere in the body, and furthermore, the gross contents of a clinically progressive hematoma, as disclosed at operation or necropsy, are usually found to be perfectly homogeneous.

From the microscopic appearance of the membrane and from negative cultural studies of the contained fluid, it does not appear

that infection can be responsible for a progressive enlargement of these lesions.

Taking all factors into consideration, it would appear that the peculiar behavior of these lesions must be the direct result of their environment. The subdural space has received surprisingly scant attention in the medical literature. Although the neurologic surgeon traverses this space almost daily, he rarely gives it much thought. Yet it is unique anatomically — a potential space lined with mesothelium, its outer wall constituted by the dura and its inner wall by the avascular arachnoid, with the cerebrospinal fluid space just beneath.* ' ' Curiously, nature has provided no obvious means of draining this space. The pericardial, pleural and peritoneal spaces all have their subserous systems of lymphatics to carry off debris. The presence of lymphatics, however, has never been demonstrated in the dura or in the arachnoid, unless one considers the subarachnoid spaces as lymphatic channels. This apparent lack of adequate lymphatic drainage from the mesothelial-lined subdural space, therefore, may provide the explanation for the curious progressive behavior of the subdural hematoma. Since the subdural space continues over the pacchionian bodies, as demonstrated by Winkelman and Fay,' it seems likely that elimination of subdural extravasations may occur at these points as well as along the nerve sheaths, provided that the extravasation is not too large.

EXPERIMENTAL STUDIES

In order to study the behavior of these lesions, attempts were made to reproduce them in animals, in spite of the failures of previous investigators.

In five dogs, a trephine opening was made over the parietal area, which was followed by a cisternal puncture to relax the unopened dura. With a fine curved hypodermic needle, from 0.7 to 3 cc. of whole, unclotted blood from the femoral vein was injected beneath the dura. A muscle graft was then placed over the puncture wound to seal it, the button of bone replaced and the wound closed. When the animals were killed, from three weeks to three and one-half months later, there was little or no gross evidence of the injected blood beneath the dura. This has also been the experience of previous investigators in this field.'

That an overlying cranial defect might in some way favor the regression of a subdural hematoma was suggested by the fact that

*Penfield, by an ingenious process, has demonstrated the presence of a small amount of yellow fluid in the subdural space of the dog and he has also described a pathologic collection in the human being.

a progressive type of lesion never follows a cranial operation. There-
fore, in order to avoid the presence of a cranial defect directly over
the experimental lesion, the following procedure was carried out on
seven dogs.

A small drill hole was made in the parietal region and was fol-
lowed by a cisternal puncture with the removal of from 5 to 10 cc. of
fluid. A curved lumbar puncture needle was then passed through
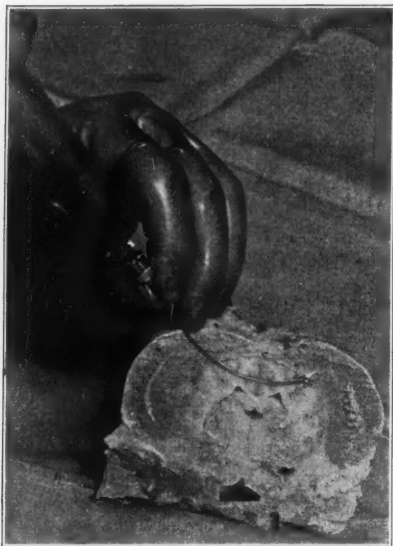
Fig. 2. Method of transcerebral injection of blood into the subdural space.

the brain across the midline until the point came to rest beneath the
intact cranial vault on the side opposite to the drill hole. At this
point from 3 to 11.5 cc. of whole, unclotted blood from the femoral
vein was injected (Fig. 2). Again, at autopsy little gross evidence
of the injected blood was found if more than a couple of weeks had
elapsed since its introduction.

In this series of experiments large dogs, weighing from 45 to 60
pounds (20.4 to 27.2 Kg.), were used in order that larger amounts of
blood might be injected. The animal into which 11.5 cc. was in-
jected died within a few hours after the experiment had been per-
formed. At necropsy, the blood was found to be generally distributed

over the hemisphere, but at no point was the clot more than 1.5 mm. in thickness. This suggested that the failure to reproduce the progressive clinical lesion might be due to failure to obtain a sufficiently thick layer of injected blood in the experimental animal.

Attention was then diverted temporarily to a study of the comparative osmotic pressures of the blood and spinal fluid.
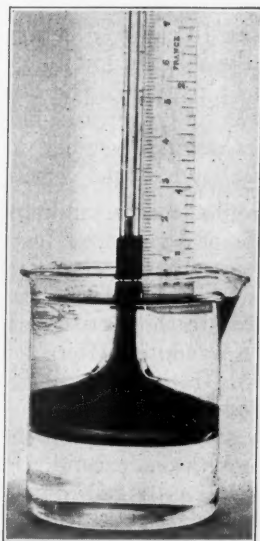
Fig. 3   Fig. 4

Fig. 3. Method of demonstrating the osmotic imbalance of the protein in the blood and spinal fluid. The beaker contains the spinal fluid, and the inverted funnel is closed with a tambour of cellophane containing the blood.

Fig. 4. Cellophane sac containing whole blood immersed in spinal fluid for the purpose of observing the increase in weight of the sac.

Semipermeable collodion membranes were first used, but were soon discarded on account of their fragility. Cellophane proved to be much more adaptable. This membrane was found to be permeable to the molecules of salts and dextrose of whole blood but not to the larger molecules of protein. In experiments in vitro it was found that when whole blood was separated from cerebrospinal fluid by a membrane of cellophane, no. 300, there was an osmotic imbalance of about 20 mm. of water in favor of the blood (Fig. 3). It was therefore assumed that 20 mm. of water represented

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the fractional osmotic pressure of the proteins of the blood against that of the proteins of the spinal fluid.

Further tests were then made. With aseptic precautions, two cellophane sacs containing whole blood taken from a patient on a fasting stomach were dialyzed against the patient's spinal fluid (Fig. 4). One test was carried out in the refrigerator at o C. and one in the incubator at 37 C. Each day, the sacs were removed from the fluid and weighed aseptically. The initial weight of the sac that was kept at o C. was 1.864 Gm. In eighteen hours, it had increased 37.1 per cent of its original weight; in forty-four hours, 57 per cent, and in sixty-six hours, 73.5 per cent. The initial weight of the sac that was kept at 37 C. was 1.286 Gm. In eighteen hours, it had increased 59 per cent of its original weight; in forty-four hours, 78.2 per cent, and in sixty-six hours, 93 per cent.

In a series of eight dogs, cellophane sacs, of known weight, containing whole blood from the femoral vein were inserted in the subdural space. The sacs with their contents were removed later and weighed in order to note any increase in weight. In five of the animals similar sacs were also placed in the rectus sheath or peritoneal cavity. In one animal, which was killed after fifty-one days, both sacs were found to be ruptured. In the remaining animals the sacs were intact when removed from three to eighteen days after implantation. After removal each sac was found to have gained from 39 to 103 per cent in weight. With one exception, the control sacs in the rectus sheath and peritoneal cavity gained more in weight than did the sacs in the subdural space.

Tests with Living Neomembrane. An opportunity of testing the permeability of the living neomembrane then presented itself. A portion of an inner cyst wall was removed from a patient at operation, two and one-half months after a cranial trauma.

Seventeen cubic centimeters of the fluid contents of the hemorrhagic cyst was dialyzed against 52 cc. of the patient's spinal fluid, the cyst wall being used as the dialyzing membrane. This preparation was made under aseptic precautions and placed in the refrigerator for sixteen hours. At the end of this time the hemorrhagic fluid had increased 2.9 per cent in volume after it had returned to room temperature. The total protein* of the surrounding spinal fluid, estimated by the Kjeldahl method, was the same after the experiment as it had been before.

*The protein content of the cyst fluid was 8.2921 per cent. The protein content of the spinal fluid was 0.854 per cent before and 0.8406 per cent after dialysis. This slight difference is within the limits of experimental error. The measurements were made by Dr. John W. Shirer.

COMMENT

The measurements indicate that the neomembrane is permeable to fluid but not to protein molecules, and that an osmotic imbalance exists which is in favor of the cyst contents.

In the light of the experiments cited, the latent interval in cases of subdural hematoma may be explained as follows:

Following a cranial trauma, hemorrhage occurs into the subdural space, probably from a rupture of one of the cerebral veins where it crosses the space to enter the sagittal sinus. A large amount of blood having escaped, becomes clotted, and within the course of a few days this clot is surrounded by a capsule of mesothelium and connective tissue growing out from the dura. That this capsule forms with remarkable rapidity is attested by clinical as well as by experimental observations.[8] The portion of the capsule next to the dura becomes invaded with nutrient capillaries from the dura and thus attains a greater thickness than does the avascular portion that is adjacent to the avascular arachnoid. The encapsulated clot then undergoes partial liquefaction, with a resultant fluid high in protein content. This fluid is separated from the cerebrospinal fluid, which is of low protein content, merely by the thickness of a few layers of cells constituting the inner wall of the cyst and the arachnoid membrane. There then results an ideal set-up for osmotic interchange. Since the neomembrane is impermeable to the large protein molecules in the hemorrhagic fluid, an osmotic imbalance in favor of the hemorrhagic fluid must exist, resulting in the withdrawal of cerebrospinal fluid into the cyst. This, of course, causes a progressive enlargement of the hemorrhagic cyst and eventually a rise in intracranial pressure.

CONCLUSIONS

1. In cases of subdural hematoma there occurs a gradual increase in the size of the lesion following its initial formation.

2. The progressive behavior of these lesions is due to their environmental conditions, particularly to the inadequacy of lymphatic drainage from the mesothelial-lined subdural space.

3. The actual increase in size of the subdural hematoma is due to an accession of tissue fluid, particularly spinal fluid.

4. This fluid is drawn into the hemorrhagic cyst through the semi-permeable arachnoid membrane and adjacent cyst wall by the osmotic tension of the blood proteins contained in the cyst.

5. It is difficult, if not impossible, to reproduce in the dog the clinical picture of subdural hematoma.

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EXPERIENCE WITH CHRONIC DEAFNESS

William V. Mullin, M.D.

The experience referred to in this title extends over a period of twenty years, during each year of which there has been but little change in treatment or in its results. Real progress, however, has been made in the diagnosis of deafness which has resulted from the standardization and improvement in quality of the tuning forks, and of adoption of the audiometer into practical use. The hard of hearing have received much benefit from various hearing aids and increased proficiency in the examination of the labyrinth has led to a better knowledge of its physiology. Because of the intimate relationship of the labyrinth with the brain, a term has been coined, the fitness of which I often question, namely, *neuro-otologist*. There is no question that the otologist knows more about the *ear* than does the neurologist, while the neurologist is better qualified to diagnose and deal with conditions within the brain. But these are two distinct fields and a hyphen does not necessarily bring these two fields closer together. Whether by his examinations alone the otologist is capable of localizing a brain lesion in my opinion is very questionable, and for this reason I think the value of the otologist to the neurological surgeon cannot be compared with that of the ophthalmologist.

My contact with deafened individuals has often made me regret whatever reputation I have had as an aurist. It is hard indeed to have a patient come, sometimes from a considerable distance, happy because he is seeing one more specialist and filled with the hope and desire for benefit, and then to have him leave in tears because it has been necessary to tell him that he has advanced nerve deafness or perhaps otosclerosis and that no local treatment will help him. In such cases the most careful painstaking advice as to the value of lip reading and of hearing aids is usually given a poor reception. One patient who later made a decided success of lip reading told me that she made six trips to the lip reading school, each time passing it by before she could compel herself to enter. Since such patients as a rule are seen only once, the entire consultation is rather unsatisfactory, and makes one inquire with Emerson: "Has science thrown any new light on our understanding of chronic, progressive deafness?" (Ann. Otol. Rhinol. and Laryngol., 40:9 1931.)

By many people hearing aids and lip reading alike are looked upon as a kind of disgrace, or as a beneficial measure for the other fellow but not applicable to one's self. The education of the hard of hearing is indeed far from its goal.

For this report I have analyzed 325 cases of chronic deafness seen during 1930. These were all of the nonsuppurative type and may be classified as follows:

Chronic catarrhal otitis media.......................... 82
Nerve deafness..150
Mixed deafness... 83
Otosclerosis... 10

A careful history was taken in all cases, this being followed by tuning fork tests, tests with conversational and whispered voice, and with the audiometer, which was considered the most satisfactory means of determining the upper tone limits. Finally there was an investigation of the patency of the eustachian tubes and when the history revealed that it was indicated a general physical examination was made.

The term, mixed deafness, was used to designate a group of cases in which the response to these tests did not fall clearly into any one of the other three classes. I believe they are typical of the class referred to by Emerson when he says: "The end result in all cases of chronic, progressive deafness is nerve deafness." In some of these cases of mixed deafness there was eustachian tube obstruction and prolonged bone conduction with a decided failure to hear high tones. In other cases there was short bone conduction with normal hearing of high tones. Certain kinds of acute inflammation within the middle ear will produce symptoms of perception deafness.

Most of the patients with chronic catarrhal otitis media came primarily to the ear department seeking relief from their symptoms referable to the ear; while the majority of patients with nerve deafness came primarily to some other department because of some general physical condition, the ear condition being discovered during routine examination of the ears, nose and throat. Cases in this group — chronic catarrhal otitis media — are worthy of much consideration.

In our enthusiasm in seeking out and removing foci of infection, and for a meticulous examination of the labyrinth, I believe the eustachian tube has been neglected. I recommend to every otolaryngologist the reading of a recent and very excellent article by A. R. Tweedie, in the Journal of Laryngology and Otology for

March, 1931, entitled "The Eustachian Tube." Tweeedie refers to the original description of Eustachius, in which he regarded the pharyngeal end of the tube and its mucous membrane as a wonderful provision of nature which serves as a janitor by protecting the various parts of the middle ear cleft beyond it.

Tweedie says that "an efficient rhinologist should certainly rob the aural surgeon of much of his work." I heartily agree with this and am an ardent advocate of treatment of the eustachian tube via the nose. In carrying this out, the Holmes nasopharyngoscope has proved to be an invaluable instrument. With it I examine the mouth of the tube in every case. In the acute cases, if they are seen before an effusion has formed in the middle ear, the condition of the nasal mucosa is ascertained and an attempt is made to clear mucus from the mouth of the tube and reduce edema and swelling by the direct application of ephedrine in oil. If there is no bulging of the drum and Weber localizes to the affected side, a bougie is inserted and an attempt is made to restore aeration of the middle ear cavity. In a considerable number of cases the necessity for myringotomy is greatly lessened.

The direct influence of septal spurs and deviations upon chronic involvement of the eustachian tube is probably negligible, but since I never use the Politzer method for inflation, whenever any obstruction impedes free passage of the eustachian catheter I do not hesitate to advise operation.

In cases of chronic catarrhal otitis media, no matter how often the eustachian catheter is inserted, it is always done under direct guidance with the pharyngoscope in the opposite nostril, as by this method there is no uncertainty about the location of the tube, or whether or not mucus is over the mouth of the tube. It should be born in mind that there are conditions in the presence of which it would be poor treatment to inflate the tube even though the symptoms indicated it. Often aspiration should be the treatment instead of inflation. The presence of hypertrophy of the posterior ends of the turbinates and their relation to the mouth of the tube and of adhesions around the lateral walls of the nasopharynx can be determined.

If the air does not pass through the tube readily, a bougie is inserted. I prefer a small olive-tipped whale bone bougie, and rely entirely upon the sense of touch rather than upon any graduations on the bougie as to the distance it is inserted within the tube. I do not attempt to use large bougies. Any manipulation that might injure the epithelium is avoided.

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I have long since given up the application of silver nitrate to the interior of the tube as I believe it has a deleterious effect on the ciliated epithelium of the mucous lining. Instead, I use a solution of resublimed iodine in liquid paraffin, this being inserted into the catheter with a medicine dropper and forced into the tube with gentle air pressure.

I emphasize this treatment because I believe in it and see good results from its use, although there is opposition to it. Thus Tweedie states: "As to any additional effect by bougies and the introduction or attempted introduction of medicated oils and vapors, I must confess that I am a heretic, although I know that skilled aurists of repute still use the same."

One condition that is not often mentioned is spasm of the eustachian tube. This is often encountered in nervous, high-strung women and when present prevents the entrance of air on inflation and sometimes resists the entrance of the bougie. In some of my cases the tube had closed upon a bougie after it was inserted and it has been difficult to release it.

Every patient with chronic deafness, irrespective of its type, is entitled to open functioning tubes if this can be accomplished. In every case of vertigo of undetermined cause the tubes should be made patent. I have some cases in which closed tubes are the sole cause of this annoying symptom.

All patients with chronic deafness who are not getting worse are improving, and every patient who still retains serviceable hearing but has closed tubes should have them treated. We are invariably asked, "Doctor, why do my ears close?" Would that we could give the correct answer. Certainly the cause of closed tubes is not entirely local. A chronic nasal discharge is too prevalent for it to be considered a cause. Atrophic rhinitis with its wide open nostrils, profuse crusting and dry glazed pharynx is not intimately connected with tubal and middle ear disease. Infection cannot be the sole basis for this condition as is evidenced by the return to normal function following severe purulent infections in the middle ear and mastoid. It would appear that we must conclude that closed tubes are a constitutional condition, since these patients are affected by such physical factors as heat, cold, barometric and temperature changes, nervous exhaustion and fatigue, intestinal disorder, the kinetic neuromuscular system bearing the brunt of such an overload. With all of these conditions must we concern ourselves in the examination and treatment of such cases.

An analysis of the 150 cases of 8th-nerve-deafness gives rather

depressing findings. Only the very deaf and the congenitally deaf came directly to the otological department. In early cases the deafness had been disregarded entirely, the condition being discovered in the routine general examination. In every case some other condition such as a chronic focal infection seemed to be present, and yet after the foci had been removed, improvement was not noted in any case. It would seem that once the 8th nerve is involved it is irreparably damaged.

It is interesting to note that there was a noticeable relationship between the presence of malignancy in some part of the body and nerve deafness.

In this group of cases of nerve deafness there were 85 males and 65 females. The average age was 46 years or more. The right ear was involved in 16 cases, the left ear in 18, while in 116 the deafness was bilateral. A positive Wassermann was found in only 4 per cent of the cases, a spinal Wassermann test being made in any case in which the symptoms indicated it. Certainly it would appear that the toxin of lues was but a minor factor in the production of nerve deafness. In several cases in which there was vertigo and nystagmus the presence of multiple sclerosis was suspected.

Eighty-three may be too large a number of cases to be included in the mixed deafness group as there may have been errors in the diagnosis. Perhaps some of these cases should have been added to the "8th-nerve-deafness" group. In some otosclerosis may have been present. But in any case, the outlook of the cases included in this group was as hopeless as in either of the other two groups.

The ten cases of otosclerosis were rather true to form. Nine ot these cases were in women. The average age in the ten cases was $32\frac{1}{3}$ years. In the majority of cases a familial history of deafness was elicited. Six of the women were married and the deafness became worse after pregnancy. Several of these patients declared they had been helped by treatment. Are we justified in trying to convince them that this apparent improvement is but a delusion? Each case was carefully studied to determine whether or not there was any endocrine dysfunction but none was found.

What, then, does this analysis show? Of 325 cases of chronic deafness seen in one year, in only 25 per cent could any kind of relief be offered by treatment, and of this 25 per cent improvement in some cases would be doubtful. Of the other 75 per cent in which advice as to lip reading and hearing aids was given or an institution for the congenitally deaf children recommended, the advice was not well received, and in the majority of instances was not followed.

The hard of hearing are deserving of especial consideration and need treatment of some kind — especially psychological. The otologist has to compete with the charlatans throughout the country who are popular because they offer these unfortunates false hopes even though at a high price.

Apology should be made for the pessimistic tone of this paper, but it expresses my feeling. I hope it may excite more interest in this problem. An earnest campaign must be carried on for the purpose of educating the public in regard to deafness, while as otologists, we ourselves should create and maintain greater interest in the eustachian tube.

PATHOLOGIC HEMORRHAGE

Russell L. Haden, M.D.

Every clinician sees at times patients who bleed without injury or who bleed excessively from a minor injury, and hence are subject to pathologic hemorrhage. The proper treatment of this condition depends on the correct classification of the homorrhagic disease and, if possible, recognition of the underlying cause. All pathologic hemorrhage is the result of an abnormal permeability of the capillaries, an increased tendency of the blood to penetrate the vessel walls, or a disturbed coagulation of the blood.

Normally, as we know, the blood does not penetrate the endothelial barrier of the capillaries, and when vessel injury occurs, a clot is quickly formed, preventing an abnormal loss of blood. According to Howell, the factors in blood coagulation are as follows: (1) prothrombin, the precursor of thrombin, is held neutral in the blood plasma by antiprothrombin (heparin); (2) on adding zymoplastic substances (tissue juice, platelets) to blood, the thromboplastin (cephalin) which these substances contain neutralize the antiprothrombin leaving the prothrombin in an active state; (3) prothrombin combines with ionized calcium to form thrombin; (4) thrombin unites with fibrinogen to form fibrin, the clot. A disturbance in any factor in the chain may lead to abnormal hemorrhage.

The important factors in blood coagulation, then are: (1) *prothrombin*, derived partly, but not solely, from platelets; (2) *antiprothrombin*, formed probably in the liver; (3) *calcium*, derived from calcium salts in the blood plasma; (4) *fibrinogen*, a globulin formed principally in the liver; and (5) *thromboplastin*, a phospholipin derived from tissue juices or platelets. This summary emphasizes the great importance of the liver which is the source of antiprothrombin and fibrinogen and of the platelets formed in the bone marrow which supply prothrombin and thromboplastin.

Increased permeability of the endothelium is also a factor in many cases of abnormal bleeding. Some observers believe that in purpura this is by far the most important factor. Normal endothelium is not permeable to normal blood. When a lowering of the viscosity of the blood occurs, as in marked anemia, there is an increased tendency for the blood to penetrate the capillary walls. In numerous conditions the capillary wall becomes more permeable

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through injury from toxic substances. Purpura developing in infections or following the use of drugs is due largely to damage to the capillary wall. Certain substances are almost specific toxins for endothelium. Classic examples of these are snake venom and bacillus Welchii toxin.

Abnormal hemorrhage may be dependent primarily upon an abnormality of the blood or blood-forming organs and in such case is spoken of as primary hemorrhagic disease. In this group are included: (1) hemophilia, (2) acute and chronic purpura hemorrhagica, and (3) hemorrhage of the newborn. More frequently abnormal bleeding is secondary to some disease in the course of which the blood or blood vessels are so altered as to lead to hemorrhage. Under the head of secondary hemorrhagic disease we include abnormal bleeding due to: (1) platelet deficiency in aplastic anemia, in intoxications such as benzol poisoning, in leukemia, and in some infections; (2) damage to capillary endothelium in Schönlein-Henoch's purpura, and in infections just as cerebrospinal or typhus fever, in drug rashes, such as that caused by turpentine, or with toxins such as snake venom; (3) a deficiency in fibrinogen due to liver disease such as cirrhosis or chloroform poisoning; (4) a decrease in ionized calcium in some cases of jaundice.

In many cases of secondary hemorrhagic disease more than one factor is operative.

A carefully elicited history and a thorough physical examination will often suggest the proper diagnosis in instances of abnormal hemorrhage, but the cases can be classified definitely only by special blood studies in addition to the routine counts and the hemoglobin estimation. The following examinations should be made in the case of every patient suffering from hemorrhagic disease:

1. *Determination of the coagulation time.* For this examination the blood must be obtained from the vein and must be free from admixture of tissue juices. The Lee and White modification of the Howell method[1] is the method of choice. Blood is obtained from the vein by means of a syringe and a fairly large needle. After the needle has been removed from the vein, 1 cc. of blood is run into a test tube 8 mm. in diameter, slightly dampened with salt solution. Clotting should be complete so that the tube may be inverted in from eight to ten minutes without altering the form of the clot.

2. *Determination of the prothrombin time.* The prothrombin time should be determined in all cases in which the coagulation time is prolonged. Varying amounts of 0.5 per cent calcium chloride solu-

tion are added to a set of tubes each containing 5 drops of oxalated plasma. The normals are as follows:

PROTHROMBIN TIME

Tube No.	1	2	3	4	5	6	7
Plasma (drops)	5	5	5	5	5	5	5
0.5% calcium chloride solution (drops)	2	3	4	5	6	7	8
Normal prothrombin time	6	8	8	10	10	12	12

3. *Determination of clot retraction.* A sample of blood is obtained by the method used for determining the coagulation time. Agitation of the specimen should be avoided as this will inhibit clot retraction. The specimen should be placed in an incubator at 37 degrees centigrade and observed for from twelve to twenty-four hours. Normally, a definite retraction is observed in one hour although the process is not complete until eighteen hours have elapsed. Retraction is often satisfactory at room temperature and may take place in a very short time. Pathologic blood may show no retraction even after days. Absence of clot retraction is usually associated with a diminution of platelets since the phenomenon is caused by some substance associated with the platelets.

4. *Enumeration of blood platelets.* An idea of the number of platelets present is obtained from a stained film properly made on a cover glass. The platelets may be satisfactorily counted by the Rees-Ecker method. The normal number is 250,000 to 300,000 per c. mm.

5. *Measurement of the bleeding time.* This determination is made by Duke's method. The lobe of the ear or the finger tip is punctured with a sharp needle or a blood lancet and the blood wiped up at regular intervals on filter paper, preferably every minute. Normally, bleeding ceases in less than three minutes, a bleeding time of over ten minutes being definitely prolonged. A diminution of platelets is nearly always present with a prolonged bleeding time.

6. *Capillary resistance test* (Leede-Rumpel test). A blood pressure band is placed on the upper arm and the pressure maintained at 100 mm. for from two to three minutes. In positive cases a crop of petechiae appears below the arm band and under it. The appearance of petechiae indicates an increased permeability of the capillary walls and is usually associated with a platelet deficiency.

In cases of jaundice the calcium time should also be determined and occasionally determinations of fibrinogen are indicated.

The typical clinical and blood findings in the various types of hemorrhagic disease are given below, and are illustrated by cases.

A. Primary Hemorrhagic Diseases

I. *Hemophilia:* An abnormal tendency to bleed, appearing early in life in the male sex and transmitted only by the unaffected females. The typical blood findings are an increased coagulation and prothrombin time with normal clot retraction, and a normal platelet count and bleeding time. The hemorrhagic tendency appears early in life; there is no bleeding from the mucous membranes but there are usually hemorrhages into the joints. The prolongation of coagulation time is seemingly due to a qualitative defect in the platelets, with an increased resistance to dissolution.

The following cases are typical examples of hemophilia:

Case 1. The patient was a boy, 6 years of age, who, following circumcision at one week, had had a severe hemorrhage from the wound which lasted for two days and was finally relieved by transfusion. He had had many hemorrhages into all the large joints and into the skin and subcutaneous tissues of various parts of the body but there was no bleeding from mucous membranes. The boy had been perfectly well except for the abnormal bleeding. The findings from the physical examination were negative except for swelling of the right elbow and the left knee. X-rays of knees and elbows revealed joint changes characteristic of hemophilia. The patient had no brothers and there was no family history of hemorrhagic disease. The blood findings were as follows:

Red blood cells, 3,790,000; white blood cells, 7,000; hemoglobin, 76 per cent, differential count, normal. Coagulation time, 2 hours (slight clot formation at one hour); prothrombin time, 45 minutes. Clot retraction, normal. Platelets, 384,000. Bleeding time, 3 minutes. Capillary resistance test, normal.

This was a typical case of severe true hemophilia in the absence of familial hemorrhagic disease. The patient was made sensitive to sheep serum and at intervals small doses of serum were administered intradermally, to induce a mild anaphylactic reaction. No improvement followed this treatment.

Case 2. A boy, 13 years of age, has bled excessively since infancy upon receiving the slightest injury. He often bleeds from one to three weeks from an injury, and has had recurrent hemorrhages into the joints. His mentality is below par and there is a speech impairment which is probably due to a cerebral hemorrhage at birth. The patient was admitted to the hospital on account of pro-

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longed bleeding following the extraction of a tooth. He was relieved by transfusion. There have been 13 known male bleeders in the family but no hemorrhagic disease has been found in the females.

The examination showed no petechiae. Examination of the joints gave negative findings. The tonsils were large and there was a slight general adenopathy.

The blood findings were as follows: Erythrocytes, 3,050,000; leucocytes, 10,500; hemoglobin, 56 per cent; differential count, normal. Coagulation time, 22 minutes. Prothrombin time, 22 minutes. Clot retraction, normal. Platelets, abundant. Bleeding time, normal. Capillary resistance test, normal.

II. *Purpura hemorrhagica (essential thrombocytopenia):* This disease may be congenital or acquired, and is found more commonly in women than in men. Hemorrhage from the mucous membranes may be the only evidence of the disease, but in addition, numerous petechiae are usually found on the body.

The characteristic blood findings are a normal or only slightly prolonged coagulation time but there is no clot retraction. The platelets are usually markedly diminished and the bleeding time much prolonged. The capillary resistance test is practically always positive.

The following cases are typical examples of purpura hemorrhagica:

Case 1. A female school teacher, 23 years of age, for two months had noticed large hemorrhagic areas and numerous petechiae on the skin following a slight injury or without injury. She had also had three attacks of nosebleed without apparent cause. Recently she had noted bleeding from the gums and also the mentrual flow had been excessive. There had been no previous infections.

The physical examination was entirely negative except for the hemorrhagic disease. There were many petechiae over the entire body and several large ecchymoses.

The blood examination showed: 3,250,000 red cells; 4,850 lucocytes; hemoglobin, 42 per cent; differential count, normal. Coagulation time, 15 minutes. Prothrombin time, not determined. Clot retraction, none. Platelets, 10,000. Bleeding time, 35 minutes. Capillary resistance test, positive.

This patient showed no improvement after viosterol and ultra-violet therapy, and numerous transfusions gave but little benefit. X-ray treatment to the spleen did not help. A few hours before the death of the patient, antivenin serum was administered with no change in the bleeding.

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In a serious acute case of purpura hemorrhagica such as this a great increase in capillary permeability evidently occurs for which treatment avails little. Splenectomy in acute cases has usually ended fatally.

Case 2. A boy, seven years of age, two weeks before admission had had a rash which was considered German measles by his father, a physician. One week previous to his admission petechiae had developed. He had had some bleeding from the nose and gums.

On admission, in addition to the anemia which was evidently present ecchymoses and petechiae were visible over the entire body. The tonsils were enlarged and cryptic. The cervical and inguinal glands were enlarged. The spleen was not palpable.

The blood examination showed: Red blood cells, 4,000,000; white blood cells, 8,500; hemoglobin, 70 per cent. Differential count: polymorphonuclears, 38 per cent; eosinophiles, 4 per cent; lymphocytes, 52 per cent; monocytes, 6 per cent. Coagulation time, 10 minutes. Prothrombin time, 8 minutes. Clot retraction, none. Platelets, 32,000. Bleeding time, much prolonged. Capillary resistance test, positive. Blood transfusion brought about a rapid diminution of symptoms. Later a tonsillectomy was performed without abnormal bleeding. After three years the child is entirely well and has had no recurrence of the abnormal bleeding.

This is evidently a case in which the decrease in platelets was due to infection and was transitory. It is very probable that the infection was tonsillar in origin.

Case 3. For two years previous to admission, this patient, a boy, 9 years old, had had several severe nosebleeds lasting for hours in each instance. He bruised easily, large ecchymotic areas being formed, and some bleeding from the gums was present constantly. The patient was unable to attend school, and other activities were much limited by the abnormal tendency to bleed.

When the boy was admitted he was suffering from a nosebleed. There were many petechiae over the entire body. The liver and spleen were not palpable. The tonsils were large and infected.

The blood findings were as follows: Red blood cells, 3,440,000; white blood cells, 4,100; hemoglobin, 64 per cent. Differential count, normal. Coagulation time, 12 minutes. Prothrombin time, 10 minutes. Clot retraction, none. Platelets, 50,000. Bleeding time, much prolonged. Capillary resistance test, positive.

A splenectomy was performed, followed by a normal convalescence. The pathological diagnosis was chronic splenitis with an unusual eosinophilic infiltration.

The patient continued to have occasional nosebleeds which, however, were not severe. He gained in weight, improved rapidly, and was able to lead a normal life which he had not been able to do before splenectomy was performed.

The platelet count rose immediately after operation and then fell and remained low.

The counts are as follows:

	Platelets	Hemoglobin
Before operation..................	50,000	64 per cent
24 hours after operation...........	150,000	55 per cent
72 hours after operation...........	100,000	65 per cent
5 months after operation..........	64,000	80 per cent
2 years after operation............	80,000	80 per cent

Case 4. A woman, 46 years of age, had had severe nosebleeds since the age of three years. At times she had unexplained hemorrhages from the gums, rectum and uterus and stated that for years she had passed blood with every stool. Two years previous to her admission linear streaks developed on the shins, followed by bleeding.

Upon physical examination no petechiae were found. The spleen was palpable but not large. There was no apparent infection. Gastric analysis showed no free hydrochloric acid.

The blood examination showed: Red blood cells, 1,980,000; white blood cells, 3,500; hemoglobin, 22 per cent. Differential count, normal. Coagulation time, 10 minutes. Prothrombin time, 10 minutes. Clot retraction, none. Platelets, 40,000. Bleeding time, much prolonged. Capillary resistance test, positive.

This patient is evidently an example of congenital platelet deficiency. A splenectomy should have been performed but the patient refused operation. Treatment had little effect on the blood condition and the clinical symptoms.

III. *Hemorrhagic disease of the newborn:* This condition which occurs only in infants during the first few days of life is characterized by spontaneous hemorrhages occurring usually not later than the second week of life. Relatively few careful blood studies have been made. The platelets seem to be normal but the coagulation and bleeding times were prolonged. Gelstron' found a prothrombin deficiency.

B. Secondary Hemorrhagic Disease

1. *Platelet deficiency:* In this condition the blood findings are much like those in purpura hemorrhagica. The following cases are typical examples:

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Case 1 (aplastic anemia). A boy 15 years of age, had been well until one month before admission when his throat became sore and began to bleed. Soon afterwards hemorrhagic areas appeared on the skin. Three weeks previous to admission, toothache developed, the neck became swollen, and the gums began to bleed. During the past two weeks the patient had passed blood in stools and urine.

The physical examination revealed many petechiae, retinal hemorrhages and several badly infected carious teeth with enlarged glands on the side of the infection. The liver and spleen were not palpable. The capillary resistance test was positive. The urine was negative.

The blood examination showed: Erythrocytes, 800,000; leucocytes, 400; hemoglobin, 13 per cent. Differential count: Polymorphonuclears, 46 per cent; lymphocytes, 50 per cent; monocytes, 4 per cent. The coagulation period was twelve minutes. The prothrombin time was not determined. Clot retraction, none. Platelets, 10,000. Bleeding time, 45 minutes. Capillary resistance test, positive.

After transfusion the patient showed much improvement. The infected tooth roots were removed. The leucocyte count remained low, however, and the number of platelets did not rise above 60,000. Death resulted from lobar pneumonia which developed two weeks after the patient was admitted to the hospital. At autopsy the diagnosis of aplastic anemia was confirmed.

In this case the abnormal bleeding was due to the platelet deficiency which, however, was only a phase of the aplastic anemia.

Case 2 (tuberculosis of liver and spleen). This patient, a woman, aged 35 years, had had recurring attacks of fever accompanied by few other symptoms. On examination the liver was found to be much enlarged and the spleen a hand's breadth below the costal margin. An exploratory operation was performed and some tissue was removed. The pathologic picture was typical of tuberculosis. The avian type of tuberculosis was suggested but not proven. Several months later this patient returned complaining of bleeding from the kidneys, uterus, nose and gums. There were many petechiae. The liver and spleen were unchanged in size.

The blood findings were as follows: Red blood cells, 3,100,000; white blood cells, 6,300; hemoglobin, 55 per cent. Differential count, normal. Coagulation time, twenty-five minutes. Prothrombin time, not determined. Clot retraction, none. Platelets, none. Bleeding time, much prolonged.

This patient responded well to transfusion and the abnormal bleeding ceased. The platelet deficiency here was probably due to the tuberculous infection of the spleen.

II. *Damage to capillary endothelium:* In this condition abnormal hemorrhage occurs without alteration in the blood.

Case 1 (Henoch-Schönlein's disease). For the past year a clerk, 25 years of age, had had recurring attacks of abdominal pain accompanied by nausea and vomiting. During each attack the large joints had been painful and red splotches had appeared on the extremities. After the first attack of pain the appendix was removed but no improvement resulted.

On admission of the patient a generalized petechial rash was present. Several joints were painful and tender on palpation. The tonsils were of moderate size. Evidence of chronic prostatitis was found and there were several infected teeth. The capillary resistance test was negative.

The blood examination showed: Red blood cells, 5,590,000; white blood cells, 11,600; hemoglobin, 102 per cent; differential count, essentially normal. Coagulation time, 9 minutes. Prothrombin time, not determined. Clot retraction, normal. Platelets, 290,000. Bleeding time, five minutes.

Following tonsillectomy and the removal of the infected teeth the patient gained 40 pounds in weight and made a complete recovery. In this case the abnormal bleeding was doubtless due entirely to increased permeability of the capillaries.

III. *Fibrinogen deficiency:* Abnormal bleeding due to a deficiency in fibrinogen is uncommon and occurs only in extreme hepatic disease. Fibrinogen is an exceedingly labile substance which seemingly is easily mobilized. A slight injury to the liver or to other tissues causes a rapid and usually marked increase in fibrinogen. Extensive hepatic injury, however, causes a decrease in the circulating fibrinogen.

IV. *Altered coagulation time due to decreased calcium ions in jaundice:*

Case 1 (obstructive jaundice). A woman, 78 years of age, had a chronic, progressive, painless jaundice. Mild diabetes and hypertension had been present for many years. On admission marked jaundice was present, accompanied by extreme itching. The liver was only slightly enlarged and the gall bladder was not palpable. The icterus index was 100.

The blood examination showed: Erythrocytes, 4,460,000; white cells cells, 9,400; hemoglobin, 78 per cent. Differential count, normal. Coagulation time, 35 minutes. Prothrombin time, 5 minutes. Clot retraction, normal. Platelets, 440,000. Bleeding time, not determined.

An exploratory operation disclosed gall stones with blockage of the common duct. The patient had been given calcium chloride intravenously peroperatively and did not bleed excessively following operation.

The convalescence was satisfactory although prolonged. The jaundice cleared very slowly. Three weeks after operation the patient had multiple hemorrhages from the intestines from which she died.

In this case the hemorrhagic disease was evidently due to the jaundice and liver disease. The coagulation time was much prolonged, with normal prothrombin time.

TREATMENT

Primary hemorrhagic disease. The treatment of *hemophilia* is most unsatisfactory. The transfusion of blood will often stop the bleeding for a time. In some cases much improvement has been brought about by making the patient serum sensitive, preferably to sheep serum and then by giving serum intradermally to induce a mild anaphylactic reaction. I have not seen any striking results from this method. More recently Birch[3] has suggested a new line of treatment with ovarian extract.

The acute phases of *purpura hemorrhagica* usually respond well to transfusion, but the platelets supplied by the normal blood live only for three or four days so that bleeding usually begins again even after relief has been obtained by the transfusion. Often, however, the patient can be tided over the acute phase of the disease by transfusion. Since in many cases infection seems to be a very definite etiologic factor in idiopathic thrombocytopenic purpura, the removal of infection is most important.

It is well known that untraviolet light and vitamin D definitely increase the platelet count; therefore ultraviolet therapy and viosterol should be used in every case.

In chronic cases of purpura due to a platelet deficiency, splenectomy must always be considered. Excellent results have been obtained by this procedure in properly selected cases. Deep x-ray therapy may also be tried. The use of serum and other thromboplastic agents is of little value in purpura and hemophilia.

Hemorrhagic disease of the new born usually responds quickly to normal blood given intramuscularly. If the bleeding does not stop after the intramuscular administration of blood, transfusion should be employed. I once transfused through the longitudinal sinus, a new-born baby who was bleeding constantly from the point of separation of the umbilical cord. Blood given intramuscularly and

other thromboplastic agents had no effect. The bleeding ceased after a few cubic centimeters of citrated blood had been run in, and did not recur.

In *secondary hemorrhagic disease* the primary cause should be treated or removed if possible, as well as the immediate cause of the bleeding. If the bleeding is due to a platelet deficiency the treatment is the same as that indicated in idiopathic thrombocytopenic purpura. Antivenin serum has been used to decrease the capillary permeability. A deficiency in fibrinogen is best treated by transfusion. In cases in which there is a deficiency of ionized calcium, the oral or intravenous use of calcium is indicated, in addition to transfusion.

SUMMARY

Cases of pathologic hemorrhage can usually be correctly classified if the various factors concerned are thoroughly studied. These for the most part are simple tests which can be done in every well-equipped laboratory. The special tests should always include: coagulation time by a correct method, retractility of the clot, platelet count, prothrombin time if the coagulation be prolonged, bleeding time and tourniquet test for capillary resistance. The different types of hemorrhagic disease present quite typical findings when grouped on the basis of these tests.

It should always be determined whether the patient is suffering from primary hemorrhagic disease or secondary hemorrhagic disease. The primary cases constitute separate clinical entities. The exact factor on which the secondary cases depend can usually be found.

The indications for the proper treatment in each case are usually clear-cut if the disease has been properly studied and classified.

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BLOOD CHEMISTRY AND THE GASTROINTESTINAL TRACT

Russell L. Haden

Much of the progress that has been made in medicine during recent years has been due to the development and clinical application of microchemical methods for the examination of the blood. Through chemical studies of the blood our viewpoint concerning the nature of some of the most serious disturbances of the gastrointestinal tract has been entirely changed and the treatment of such disorders has been revolutionized, with great advantage to the patient. The clinical conditions in the case of which blood chemistry studies are most important are those conditions which are associated with disturbances in motility accompanied usually by an abnormal loss of the gastrointestinal secretions, such as: (1) obstruction of the (a) small intestine, (b) pylorus, and (c) esophagus; (2) vomiting without obstruction; (3) fistula of the upper intestinal tract; (4) prolonged diarrhea from any cause; (5) paralytic ileus; and (6) acute peritonitis.

In all of these various clinical conditions a rather characteristic toxemia is present and in all of them, also, the chemical changes which take place in the blood and urine are of a somewhat similar nature. Intestinal obstruction is a condition which is found frequently and has been intensively studied for many years. Long before it was known that characteristic chemical changes take place in the blood, the toxemia of intestinal obstruction was considered to be due to the absorption of putrifying organic material from the lumen of the obstructed gut. Hartwell and Houget in 1910[1] concluded that dehydration was the most important factor in the toxemia of intestinal obstruction because the life of a dog in the case of which the small intestine had been obstructed experimentally could be prolonged by the administration of fluid in the form of a physiologic saline solution. In 1914 Tileston and Comfort[2] observed a marked increase in the nonprotein nitrogen of the blood in patients suffering from intestinal obstruction. This observation was verified by Whipple and his coworkers[3] in an experimental study of intestinal obstruction. Whipple[4] also found an increased destruction of protein as evidenced by the increase in excretion of nonprotein nitrogen, and concluded that the existing toxemia was due to the absorption of a toxic protein derivative from the wall of the obstructed gut. The other constituents of the blood showed no significant variation from normal.

Further clinical and experimental studies by Haden and Orr[5] showed, in addition to changes in the nitrogenous bodies, very striking variations in the blood chloride and bicarbonate. After experimental obstruction had been brought about in which the changes could be followed from the onset, there was found to be a progressive fall in the blood chlorides. As the chlorides are lost there is usually a rise in the carbon dioxide capacity of the plasma since the sodium which is left behind as a result of the loss of chloride combines with the carbon dioxide which is constantly present, thus increasing the circulating sodium bicarbonate. The level of the bicarbonate is very variable since it is dependent upon several factors other than the release of the sodium from its combination with the chloride. The fall in chloride is certainly partly due, and probably largely due to the mechanical loss through vomiting. At the same time dehydration increases. As this process continues an increase in protein destruction is shown by an increase in the nonprotein nitrogen of the blood and the urine.[6] The mechanical loss of fluids and salts with consequent dehydration may be largely responsible for the clinical picture and laboratory findings in cases of intestinal obstruction, yet it is also possible that the toxemia may be due, in part at least, to the absorption of some toxic body or bodies which destroy tissue protein. The increase in nonprotein nitrogen is certainly not due entirely to a retention from kidney insufficiency. The sugar and other constituents of the blood show little variation from the normal. The marked decrease[6] in the oxygen saturation of the venous blood is due largely to the slowed circulation rate, although it is conceivable that some reducing body may be a factor also.

The characteristic changes in the blood in the presence of intestinal obstruction, then, are (1) dehydration, (2) hypochloremia, (3) alkalosis, (4) increased nonprotein nitrogen, (5) accelerated tissue catabolism with increased nitrogen excretion, and (6) decreased oxygen saturation of the venous blood. In simple intestinal obstruction which has been brought about experimentally, a toxemia may be prevented by supplying sufficient fluid daily from the onset of the obstruction, in the form of physiologic salt solution; when the toxemia is well advanced the condition may be relieved by giving a hypertonic solution.[7] In clinical work often the dehydration has become very marked and the chloride store of the body greatly depleted, before the patient is first seen; in such cases it is wise to give a 3 per cent solution of sodium chloride which should be administered in 10 per cent glucose since food is always necessary. An operation should never be attempted in the case of

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a patient in whom an intestinal obstruction is present until a sufficient amount of fluid and salt has been given to overcome the dehydration and hypochloremia.

In the presence of pyloric obstruction[8] the chemical changes are the same as those which are characteristic of intestinal obstruction. Pyloric obstruction develops more slowly than intestinal obstruction and is often allowed to progress for a longer time before operative interference is instituted. The alkalosis and hypochloremia are usually more marked since there is a greater loss of chloride by vomiting. The dehydration, the increase in nonprotein nitrogen, and the decrease in oxygen saturation of the blood, are striking. This condition should be treated in the same way as intestinal obstruction.

Experimental obstruction of the cardia and lower end of the esophagus[9] causes dehydration, an extremely rapid rise in the nonprotein nitrogen of the blood, and a decrease in oxygen saturation, but not much change in the chloride or carbon dioxide combining power of the plasma. The toxemia which may accompany this condition can also be entirely prevented by the proper use of a salt[10] solution. A case of this type is seldom seen clinically.

A fistula[11] [12] in the upper intestinal tract will bring about the blood changes which are characteristic of intestinal and pyloric obstruction. In this case there is an excessive loss of fluid and chloride, the nonprotein nitrogen rises rapidly and dehydration is very marked. The extent of these changes can be gauged only by a chemical study of the blood and the treatment must be based on the findings.

Prolonged vomiting from any cause such as the toxemia of pregnancy[13] will produce the same chain of events. In every case of vomiting the blood should be carefully studied and the treatment which is indicated by the findings should be given. In the case of paralytic ileus definite changes are often found in the blood although not to so marked a degree. Here the use of a hypertonic solution is of value not only for its general effect but especially for its marked effect in stimulating peristalsis.[14]

In the presence of peritonitis[15] the chloride content becomes less. In this case also the nonprotein nitrogen is increased and dehydration develops. For this condition the proper use of salt solution is of the greatest value just as it is in an uncomplicated case of paralytic ileus.

The chemical changes in the body which are the result of diarrhea and vomiting have been studied by Hartmann.[16] In the case

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of diarrhea much fluid may be lost, causing a dehydration which may be serious enough to result in renal insufficiency. If there is no vomiting, the blood chemistry problem, as far as the acid-base balance is concerned, is quite different from that which is found in a case of intestinal obstruction. The bicarbonate is decreased and the chloride is increased; therefore the administration of sodium bicarbonate solution instead of sodium chloride solution is indicated.

If both vomiting and diarrhea occur a decrease in bicarbonate is evidenced by the fall in carbon dioxide combining power, and a decrease in the chlorides if the gastric secretions contain free hydrochloric acid. In such conditions, however, often very little hydrochloric acid is secreted so that the fall in bicarbonate is much more marked than is the fall in chloride.[16] Here again the indications for treatment are demonstrated only by a careful study of the blood chemistry.

TABLE I

Clinical Condition	Dehydration	Non-Protein Nitrogen	Sodium Chloride	Carbon Dioxide Combining Power	Treatment Indicated
Intestinal obstruction	+++	+++	---	+++	Hypertonic (1 to 3%) sodium chloride in 10% glucose solution.
Pyloric obstruction	++++	++++	----	++++	Same.
High intestinal fistula	+++	+++	---	+++	Same.
Paralytic ileus	+	+	-	0	Hypertonic (3%) sodium chloride solution.
Peritonitis	++	++	-	-	Hypertonic (1 to 3%) sodium chloride in 10% glucose solution.
Diarrhea only	+++	+++	+	---	Sodium bicarbonate (5%) intravenously.
Diarrhea and vomiting	+++	+++	0	---	Same.
Cardiac obstruction	++++	++++	-	-	Sodium chloride (1%).

In table I the characteristic changes which take place in the presence of the conditions which have been discussed, are summarized, and the preferred treatment is indicated in each case.

SUMMARY

In all cases of disturbances in motility of the gastrointestinal tract of the types described in this paper, the ideal procedure is to determine:

1. The extent of dehydration, which is done by the use of the hematocrit, and by the estimation of the amount of plasma protein.

2. The amount of circulating bicarbonate, which is done by estimating the carbon dioxide combining power of the plasma.

3. The amount of plasma or whole blood chloride.

4. The level of nonprotein nitrogen in the whole blood.

In cases of intestinal and pyloric obstruction the chlorides are usually lost, out of all proportion to other elements, indicating the

administration of a hypertonic solution of sodium chloride, with glucose preferably. Similar treatment is indicated in excessive vomiting in the absence of obstruction or of diarrhea, and also in cases of paralytic ileus.

Cases of cardiac obstruction in which concentration is evident, without loss of salts, are best treated by the administration of 1 per cent sodium chloride given intravenously.

If dehydration is due to diarrhea only or to diarrhea accompanied by vomiting with little hypochloric acid in the gastric secretions, the blood shows an increase in chloride but a great decrease in sodium bicarbonate. The condition must be treated by the intravenous administration of sodium bicarbonate with or without glucose.

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INTERPARIETAL HERNIAS

William E. Lower and N. Fred Hicken

The term "interparietal hernia" is used collectively to designate a group of rather unusual hernias which are located in the inguinal region between the various layers of the abdominal parietes. Anatomically, these hernias may be classified as follows: (1) Properitoneal hernia, that type in which the hernial sac lies between the peritoneum and the transversalis fascia; (2) interstitial hernia, in which the sac lies between the transversalis fascia and the transversalis, internal oblique, or external oblique muscles; and (3) superficial hernia, in which the sac is situated between the aponeurosis of the external oblique muscle and the integument.

Since interparietal hernia has been spoken of by all authorities as being of rare occurrence it is surprising to find that 587 cases have been reported in the literature. The inability to diagnose this condition pre-operatively and the consequent high mortality rate indicate how superficial is our knowledge of this type of hernia. Since the days of Thomas Bartholin (1661), many noted surgeons have been chagrined because they failed to recognize this type of hernia at the operating table, the mistake being revealed at necropsy.

Because of these considerations, we feel justified in presenting a clinical study of interparietal hernias based on cases observed at the Cleveland Clinic and those reported in the literature.

Two Cases of Interstitial Hernia

Case I.— The patient, a truck driver, aged fifty-eight, reported at the Cleveland Clinic April 27, 1929, complaining of pain occurring low in the left side.

Four years previously, a severe pain suddenly developed in the lower left abdominal quadrant radiating downward toward the bladder and penis. The paroxysm lasted about thirty minutes and then subsided, leaving him perfectly well. There had been no nocturia, frequency, burning on urination, urgency, nor hæmaturia, and the urine had never contained any gravel.

Three months later a similar attack occurred, and since then the attacks had progressively increased in frequency and severity. Most of the paroxysms were initiated by work, exercise, lifting, or straining, and were always associated with the act of defecation. When the patient lay down, the pain immediately disappeared, often recurring, however, as soon as he stood up. He had never observed any swelling in the groin, and emphatically denied being

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"ruptured." Both testicles had always been in the scrotum. The day before his admission to the clinic he had an attack of severe pain in the left groin and felt nauseated but did not vomit. The pain was intense while he was working, but subsided when he assumed a recumbent position. Some soreness was present in the region of the left groin.

The general physical examination showed a well-nourished adult male. The temperature was 97.6°, the pulse rate 64, and the blood-pressure 135/100. The pupillary reactions were normal, the teeth were in good condition, the tonsils atrophic, and the heart and lungs were normal. The abdomen was symmetrical, slightly distended, and presented the appearance of generalized rigidity. The patient complained of slight tenderness in the left groin above Poupart's ligament near the internal inguinal ring, and when pressure was applied at this point the patient felt a sense of soreness and said that he could feel "something slipping back into the abdomen." No masses or swellings could be detected. Both external rings were slightly dilated, but no hernial sac could be felt, and no impulse was transmitted during the act of coughing. Cystoscopic and pyelographic studies showed that the genito-urinary tract was normal, and all laboratory studies gave normal values. Gastrointestinal rontgenograms failed to indicate any point of intestinal obstruction.

We felt that we were dealing with a case of partial intestinal obstruction produced by some mechanical constriction in the region of the internal inguinal ring. We were convinced, however, that the cause was not a common direct or indirect inguinal hernia. As conservative treatment did not result in improvement, operative intervention was deemed necessary.

An oblique incision was made in the lower left quadrant a half-inch above and parallel to Poupart's ligament. The aponeurosis of the external oblique muscle was exposed, but no inguinal hernia was palpable. On palpation in the region of the internal inguinal ring, a "gurgling sensation" could be felt, and it seemed as if a "loop of bowel" suddenly receded into the abdomen. The external oblique muscle was incised just mesial to the course of the inguinal canal, and a small empty hernial sac was found between the external and internal oblique muscles. By careful dissection the sac was isolated and it was found to have passed through the internal and external oblique and transversalis muscles, piercing the transversalis fascia, and opening into the peritoneal cavity about one centimeter to the left and just above the internal inguinal ring. There was no communication with the inguinal canal. The spermatic cord and

vessels could be seen entering the inguinal canal through the internal ring, and no inguinal hernia was demonstrable. The orifice of the hernial sac readily admitted the thumb, and the neck was thick and elastic but easily dilatable. The belief seemed reasonable that any increased intro-abdominal pressure would dilate the neck of the sac and permit the intestines to enter. No incarceration, however, had taken place. The neck of the sac was securely ligated, the various layers of the abdominal wall were closed, and the patient made an uneventful recovery.

Case II.— The patient, a woman, aged forty-one, the mother of three children, reported at the Cleveland Clinic on May 13, 1930, complaining of abdominal pain.

For the past six years she had suffered from flatulence, abdominal distention, and pains in the upper right quadrant. On two occasions there had been "chills and fever," associated with some tenderness over the region of the gall-bladder. Five years before this examination cholecystostomy had been performed, and a few stones and much pus had been found. Since then abdominal pain and tenderness had recurred in the old scar. During the three months previous to her entering the Clinic, pain had been present in the right inguinal region which was accentuated by working or by lifting heavy objects. At times the patient thought she could feel a slight swelling in the groin, but when questioned, she admitted that it was only her "imagination." At times the distress became so intense that she would be compelled to lie down, and immediately she would feel a peculiar "sliding sensation" in the right groin, and the pain would disappear. She denied having been ruptured.

Examination revealed a well-developed adult female. The temperature was 99.2°, the pulse rate 92, and the blood-pressure 148/94. The pupils were equal, with normal reactions. The heart and lungs were essentially normal. A scar in the upper right rectus muscle was indurated, tender and inflamed. There was some localized muscular rigidity but no feeling of fluctuation. The gall-gladder could not be palpated on account of the tenderness in this region. In the right groin, just above the external inguinal ring, was a small swelling which increased in size on straining and to which a definite impulse was imparted by coughing. The external ring was small, and no enterocele could be palpated in the canal. Both femoral rings and the left external inguinal ring were normal.

The pre-operative impression was that an abscess of the gall-bladder was pointing in the old cholecystostomy scar, and that an interstitial hernia was present in the right inguinal region. The

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latter diagnosis was made because of our experience with the previous case.

A transverse incision was made over the right inguinal canal. A probe was readily introduced into the canal through the external ring, and no enterocele or obstruction was encountered. On palpation, a small tumor-like mass could be felt just near the outer side of the canal. An incision was made directly over the swelling, and as soon as the fibres of the external oblique muscle were separated, a small, partially collapsed hernial sac was seen lying between the two oblique muscles. When this sac was opened, a few tags of omentum were disclosed. The sac was carefully dissected free from the adjacent structures, to which it was fairly adherent. It lay in direct apposition to the lateral walls of the inguinal canal, pierced the internal oblique and transversalis muscles, as well as the transversalis fascia, and opened into the peritoneal cavity by its individual orifice, situated just lateral to and above the internal inguinal ring. The round ligament entered the inguinal canal through a normally located inguinal ring, and there was no communication between this canal and the interstitial hernia. The sac was ligated, the aperture through the abdominal wall was closed, and the patient made an uneventful recovery.

In both of the cases described above the condition was caused by a simple interstitial hernia, the sac in each instance being contiguous to but not communicating with the inguinal canal, each having its own separate orifice. Kronlein has discussed this type of hernia to which, because of its juxtaposition to the inguinal canal, he gave the name "para-inguinal interstitial hernia."

As there are three anatomical varieties of interparietal hernia — properitoneal, interstitial and superficial hernias, these will be discussed separately.

PROPERITONEAL HERNIA

The first authentic report on interparietal hernias was made by Bartholin in 1661, but his description was not sufficiently complete to permit classification. In 1779 Petit described a group of hernias which were situated within the interstices of the abdominal wall. In 1839 Parise saw a hernia in which the sac was situated between the peritoneum and the transversalis fascia, and in 1851 he described it under the name of "intra-iliac hernia." In 1864 Streubel collected reports of fourteen cases. The most important work however was done by Kronlein, a report of which was published in 1876. He collected and analyzed twenty-three cases which had been reported

up to that time; he carefully described the anatomical positions and clarified the etiologic factors concerned in their production, giving to this type of hernia the name "hernia inguinoproperitonealis." In 1895 Breiter, a pupil of Kronlein, collected thirty-six additional cases, and in 1900 Goebell brought the literature up to date, presenting a series of sixty-nine cases. Since that time we have been able to gather reports of fifty cases from foreign and English journals, making a grand total of 119 cases of properitoneal hernia thus far reported.
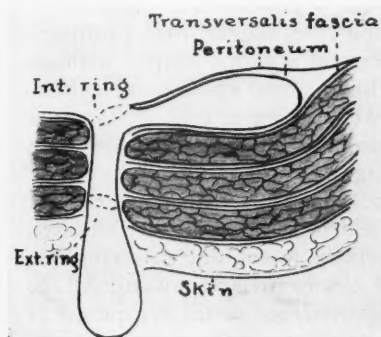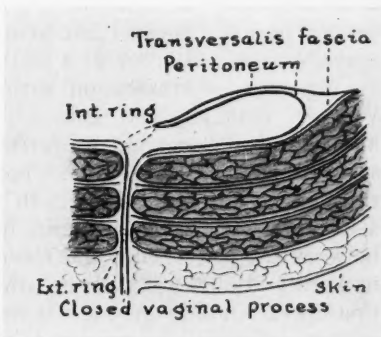

| Fig. 1 | Fig. 2 |
| Bilocular properitoneal hernia | Monolocular properitoneal hernia |

Definition and Anatomical Considerations.— Since properitoneal hernia usually occurs in the form of a diverticulum from the walls of an inguinal or femoral hernia, cases of this type are generally designated inguinoproperitoneal or cruroproperitoneal hernias. Moynihan reserves the name "properitoneal hernia" for those which fulfill the following conditions: (1) The hernial sac must be bilocular, one loculus extending down into the inguinal or femoral canal, and the other spreading out between the peritoneum and the transversalis fascia. (2) The two loculi must communicate with each other. (3) Both loculi must open into the peritoneal cavity by means of a common orifice — either the internal inguinal or the femoral ring.

Moynihan, Halstead, and many other authorities agree that all properitoneal hernias are bilocular, as shown in fig. 1. However, we have been able to collect fourteen authentic cases in which only one sac could be demonstrated, as illustrated in fig. 2. At operation, the enterocele was found to have entered the inguinal canal through a normal internal inguinal ring, but instead of extending down the

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inguinal canal, the hernial sac had spread out between the fibres of the peritoneum and transversalis fascia. The process vaginalis which continued down into the scrotum or into the labia was completely closed, and no hernia was present. These, therefore, were typical monolocular hernias. Goebell found that of sixty-nine cases of pro-peritoneal hernia sixty were bilocular and nine were monolocular. Novaro, who in 1921 made a careful study of this type of hernia, is convinced that monolocular forms do exist.

Halstead maintains that a properitoneal hernia always occurs as a diverticulum or outpouching from a pre-existing inguinal or femoral hernia. However, the following cases suggest that a properi-toneal hernia can occur as a distinct and separate entity, without having any communication with the inguinal or femoral canals. Wagner, Brunner, and Englisch each report a case of inguinal hernia and a coexisting properitoneal hernia. These hernias were separate and distinct, each opening into the abdominal cavity through an individual orifice. In 1902, Howlett reported a case of a bilocular properitoneal hernia in which both loculi were situated between the peritoneum and transversalis fascia, one sac extending upward and outward and the other downward and inward. At the first operation only one sac was recognized, but as the symptoms of nausea and vomiting persisted, a second operation was performed which revealed a loop of strangulated bowel in the second properi-toneal sac. This is a good example of a properitoneal hernia occur-ring outside of the inguinal canal but lying adjacent to it.

It would seem, therefore, that properitoneal hernia, in both the monolocular and the bilocular forms, may be classified as follows: (1) Inguinoproperitoneal hernia, which occurs as a diverticulum from a pre-existing inguinal hernia. (2) Cruroproperitoneal hernia, which occurs as an outpouching of a femoral hernia. (3) Simple pro-peritoneal hernia which is independent of the inguinal or femoral canals.

The anatomical positions which may be assumed by the properi-toneal sac must be clearly understood if these hernias are to be treated surgically. Usually it occupies one of three positions: (1) It may pass upward and outward toward the anterosuperior iliac spine. This is the usual position. (2) It may pass directly backward, and occupy the iliac fossa. This form is often mistaken for a retro-peritoneal hernia, and its relation to the inguinal canal is forgotten. (3) It may pass downward and inward to the side of or in front of the bladder. This type has been called the inguinovesical or pre-vesical hernia.

Etiology.— Precise knowledge concerning the formation of properitoneal hernia is wanting, as is attested by the number of theories which have been advanced, of which only a few of the most logical can be discussed.

After making a meticulous study of the inguinal canal, Eppinger decided that its anatomical structure was such that it predisposed to the formation of properitoneal hernia. He arbitrarily divided the canal into three portions: (1) the innermost section, which extends from the internal inguinal ring to the point where the infundibuliform fascia pierces the transversalis muscle. In this portion of the canal the transversalis fascia is firmly adherent to the transversalis muscle, but only a few fibrous tissues connect it with the peritoneum, this space being filled with loose, non-resisting fatty tissue. (2) The middle portion of the canal, which is 10 to 12 centimetres long, and is surrounded by the internal oblique and transversalis muscles. Here the muscular reinforcement precludes the formation of interparietal hernias. (3) The anterior segment of the canal, which corresponds to the space between the internal oblique muscle and the external inguinal ring. The two oblique muscles are loosely attached to each other by strands of connective tissue, and the interstices are filled with loose, yielding, adipose tissue. It is thus evident that the weakest points in the inguinal canal are at the inner and anterior segments, and it is here that interparietal hernias are encountered clinically.

It has been observed that properitoneal hernia frequently is associated with conditions which prevent the normal descent of the hernial sac. Macready, Streubel, and Kronlein noticed that an ectopic testicle situated in the inguinal canal or just outside of the external inguinal ring obstructs the descent of a congenital hernia, and if the impulses from above continue, the hernial sac is forced between the layers of the abdominal wall. It must be remembered, however, that properitoneal hernias are found in males with normal testicles, and have been reported also as occurring in women; hence some other factors must operate in their production. Von Mosetig-Moorhof insists that a narrowing of the external inguinal ring permits the bowel to descend into the dilated inguinal canal but prevents its descent through the external ring, and therefore, the hernial sac insinuates itself between the abdominal muscles. In support of this theory, Tillaux describes a case of properitoneal hernia in which the opening of the external ring was so small that it barely permitted the passage of a nerve, much less an enterocele. Butz and Bramann cite a case in which the external ring was entirely absent, yet a properitoneal hernia was found. Moynihan

believes that a defective formation of the scrotum results in an ectopic process vaginalis and testes, with resulting obstruction to the descent of a coexisting congenital hernia. Coley encountered a case in which a hydrocele in the canal of Nuck acted as a barrier to the descent of a congenital enterocele and caused a properitoneal hernia. Streubel maintains that an ill-fitting truss which permits the canal to remain open and merely presses over the external ring causes a mechanical obstruction which predisposes to the formation of interparietal hernia. According to Birkett, this theory is untenable, as malposition of a truss is very common and the occurrence of this hernia is infrequent.

It has been suggested that a narrowing of the internal inguinal ring might prevent the replacement of a large hernia into the peritoneal cavity. Gosselin and Streubel pointed out that if the internal inguinal ring was constricted and pressure was exerted from below, as in repeated and indiscriminate taxis, it might cause a bulging of of the neck of the sac between the peritoneum and the transversalis fascia. By pressure over a large scrotal enterocele, Corner was able to force the intestines into a properitoneal sac, and by pressure over the properitoneal swelling, the hernial content immediately descended into the scrotum. While doing the herniorrhaphy, he was able to repeat this phenomenon, and found a narrow internal ring which diverted the scrotal contents into the properitoneal sac. Many of the so-called reductions en masse were merely instances in which the scrotal hernia was forced into a preformed properitoneal sac. The accepted explanation of reduction en masse is that an inguinal or crural sac, by repeated and forcible manipulation, is separated from its surrounding structures, and is invaginated or pushed back into the abdominal cavity without disturbing the mutual relationship between the sac and its contents. The reduced hernia always lies outside of the peritoneum.

To us it seems that the difficulty encountered in separating a hernial sac from its surrounding structures during herniorrhaphy would preclude dislocation of the hernial sac en masse by simple taxis. Streubel and Halstead believe that such cases of reduction en masse are merely the transference of the content of a scrotal or crural sac into a preformed properitoneal sac. Moynihan reviewed the specimens of reduction en masse in Guy's Hospital Museum, and concluded that most of them were from cases of properitoneal hernia. In studying the reports of cases of reduction en masse, we found that the description of the operative findings was so meager that the true anatomical position of the sacs could not be determined. We agree with Halstead and Moynihan, however, that examples of

true reduction en masse are rare, and that most of the cases which purport to be of this nature are really cases of properitoneal hernia.

In contrast with the theory of the mechanical origin of properitoneal hernia are the arguments of those who believe that all hernias are congenital. Rokitansky pointed out that in many cases small peritoneal pouches or diverticula could be seen in the immediate neighborhood of the internal inguinal ring; these, he believes, constitute the anlage of properitoneal hernia. Brunner, Englisch, and Wagner also noticed these small peritoneal pouches, and thought them responsible for interparietal hernias. In 1884, Wagner confirmed his convictions by finding a case of inguinal hernia with a coexisting properitoneal hernia which lay adjacent to the inguinal canal but did not communicate with it. Russell maintains that all hernias are congenital, and that the process vaginalis can be caught up between the layers of the abdominal muscles and form any variety of interparietal hernia. In a series of 200 post-mortem examinations, Raw and Murray found sixty-eight peritoneal diverticula, fifty-two of them being femoral, thirteen inguinal, and three umbilical. Murray believes that when these congenital diverticula or pouches exist, the occurrence of hernia depends on the size of the opening and the strength of the muscles that protect the orifice.

Coughlin's anatomical studies of adults and Moynihan's of fetuses revealed that in 22 per cent. of necropsies they could clearly demonstrate deep peritoneal pouches or fossæ near the obliterated hypogastric artery which easily could have developed into properitoneal hernias.

Kirchner reports a case of such a properitoneal hernia arising in Hesselbach's triangle as the result of a peritoneal diverticulum near the obliterated hypogastric artery. How can the occurrence of multiple hernias in the same individual be explained unless the theory of their congenital origin is accepted? Bainbridge operated on a woman in whom six separate and distinct hernias were present. Congenital malformation of a hernial sac is evident in the bifid or pantaloon hernias of Halstead, in which the inguinal sac is divided into two compartments like a pair of trousers and opens into the abdominal cavity through a normal internal inguinal ring.

Schmidt demonstrated that there might be a congenital dislocation of the internal inguinal ring upward and outward. As a result of the displacement, the spermatic cord would be too short to reach the scrotum, and an ectopic testicle would result. He convinced Oberst, Trendelenberg, Zeller, and Link that this theory was correct, but we have been able to collect only three cases which substantiate this view, those of Schmidt, Bramann, and Holder.

It must be self-evident, therefore, that the pathogenesis of properitoneal hernia cannot be ascribed to a single cause, but rather to a combination of many factors.

Incidence and Sex.— The incidence of properitoneal hernia is a subject of much controversy. Bull and Coley found but one case out of 5,000 consecutive herniotomies, while Kirchner observed two cases out of 500. We believe that the frequency of properitoneal hernia is greater than these figures indicate, and that many cases have remained undiagnosed.

Both sexes are affected, but the condition is much more common in the male than in the female because of the greater percentage of congenital anomalies which are present in the male inguinal region. Of the cases collected since 1900, thirty-three have been reported in males and nine in females, and in eight the sex was not mentioned.

All ages are involved, the youngest patient being fifteen and the the oldest seventy-five. The average age for the male is thirty-eight; the greatest number of cases occur between the ages of thirty and fifty years, which is the period of greatest muscular activity. In women the average age is fifty-five.

The right side is involved more frequently than the left, because of the greater percentage of congenital anomalies associated with the later closing of the right vaginal process. In Goebell's series of sixty cases, thirty-seven occurred on the right side and twenty-three on the left. In our collection, twelve were found on the right side and eight on the left, the side not being mentioned in thirty cases.

Symptoms.— There is no pathognomonic sign or symptom that will lead to the diagnosis of properitoneal hernia. Fully 90 per cent of the patients will present themselves with the clinical syndrome of acute intestinal obstruction. They may have had a reducible inguinal or femoral hernia of long standing. Following an apparent reduction, the patient becomes nauseated and vomits, the abdomen becomes distended, and the bowels constipated. On examination, an irreducible inguinal or femoral hernia may be found, with some tenderness over the region of the internal inguinal ring, but as a rule no swelling occurs above Poupart's ligament. Of Breiter's thirty-six cases, a swelling was felt above Poupart's ligament in twenty-two. Moynihan disbelieves Breiter's contention, and corroborates his views by an examination of all specimens of properitoneal hernia in the museum of Guy's Hospital in which he found the position of the interstitial sac to be such that it precluded recognition on abdominal examination. In rare instances the content of the inguinal hernia may be reduced into the properitoneal sac,

and then the diagnosis is obvious. In those cases in which there is no accompanying inguinal or femoral hernia, it is usually impossible to make a pre-operative diagnosis.

It is only by operation or post-mortem examination that the true nature of the hernia is revealed. Many surgeons have performed a herniotomy for strangulated inguinal hernia, removed the sac, and closed the wound, but when, to their surprise, symptoms of obstruction persisted and a subsequent operation was performed, a strangulated properitoneal hernia was found.

Of the cases reported since 1900 that we have collected, thirty-four were strangulated or incarcerated, four were reducible, and in twelve no history was given. The failure to make an early diagnosis and the resultant delayed operative intervention has resulted in a high rate of mortality. Torrey in 1888 reported thirty-five cases of strangulated properitoneal hernia, with an operative mortality of 80 per cent. In our series of fifty herniorrhaphies, there were ten deaths, and in twenty cases the results were not known, making a mortality of 20 per cent or more.

The treatment of properitoneal hernia will be considered jointly with the treatment of the other types of interparietal hernias.

Interstitial Hernia

The two cases we have presented are typical of this group of interparietal hernia. (See cases I and II.)

From an autopsy specimen, Hesselbach, in 1814, presented an excellent illustration of this variety of hernia, with the sac lying between the internal and external oblique muscles. In 1812, Cooper observed and, in 1827, published an account of the first successful herniotomy for a strangulated interstitial hernia, the sac being situated between the two oblique muscles. In 1893, Macready was able to gather 163 cases of this form of hernia from the records of the London Truss Society, but as these cases were not verified by autopsy or operative findings, their diagnosis is uncertain. Interstitial hernia in women was first described by Berger in 1891, and Auvray in 1900 reported fourteen such cases. In 1900 Goebell collected 115 cases of interstitial hernia which had been found at operation or post-mortem examination. We have been able to gather sixty-five cases from the literature and have made two personal observations, making our series a total of sixty-seven. These, added to the figures reported by Macready and Goebell, make a grand total of 345 known cases of interstitial hernia.

Definition and Anatomical Considerations.— In interstitial hernia the sac burrows its way between the layers of the abdominal wall, and may be found in any of the following positions: (1) Between

the transversalis muscle and fascia: (2) between the transversalis and internal oblique muscles; (3) between the fibres of the internal oblique muscle; or (4) between the internal and external oblique muscles, the latter being by far the most common position. Many writers contend that the only variety seen is the form in which the sac lies between the two oblique muscles. Moynihan even goes so far as to deny the possibility of other forms because he believes the anatomic structure of the inguinal canal is such as to preclude the formation of intermuscular hernias in this section of the canal.
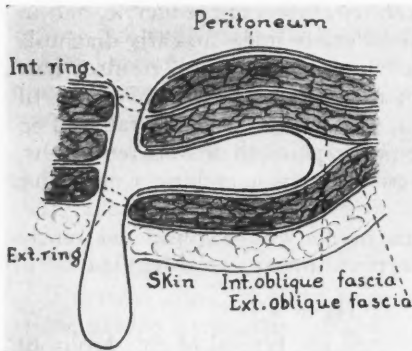

Fig. 3
Bilocular interstitial hernia
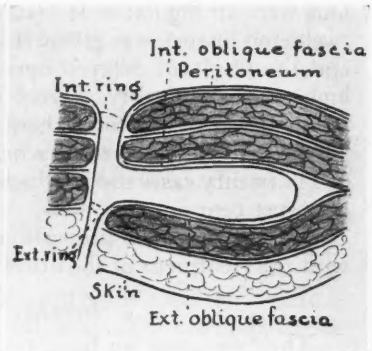
Fig. 4
Monolocular interstitial hernia

We have been able, however, to collect authentic cases of all four types of interstitial hernia mentioned above. Goebell reports eleven cases in which the hernial sac was located between the transversalis muscle and fascia, typifying group 1. He also found fifteen cases in which the hernial sac lay between the external oblique muscle and the transversalis fascia, the internal oblique and transversalis muscles being deficient in this area. As in every one of his cases the hernia was incarcerated, the exact anatomical position was determined during the operation. Coley and Sultan each describe a case in which the sac is situated between the fibres of the internal oblique and the transversalis muscles (group 2). Illustrative of group 3, Goyrand, Berger, and Venturoli have seen the hernial sac completely surrounded by the filaments of the internal oblique muscle. Goyrand, indeed, considers it characteristic, and believes that the hernial sac insinuates itself between the muscle fibres. In Berger's case, the man had a congenital monolocular hernia of the right side, and the hernial sac was surrounded by muscular fibres of the internal oblique muscle. Venturoli had to sever the

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filaments of the internal oblique muscle in order to release the incarcerated hernial sac. Group 4 consists of the intermuscular hernias most commonly encountered — those situated between the two oblique muscles. Thus it seems to us that there is definite clinical evidence as to the existence of all four varieties of interstitial hernia.

Moynihan, Halstead, and Watson all assert that an interstitial hernia must be bilocular (fig. 3). One loculus must extend down the inguinal canal through the external ring and may or may not descend into the scrotum; the other loculus must pass out between the external and internal oblique muscles, and both loculi must communicate with each other and open into the peritoneal cavity through the internal inguinal ring. However, all interstitial hernias are not bilocular, for cases have been described which demonstrate that both trilocular and monolocular forms exist.

In Ehler's interstitial hernia there were three sacs, one extending between the internal and external oblique muscles, one between the skin and superficial fascia, and the third descending into the scrotum. All three loculi communicated with each other and opened into the abdominal cavity through the internal inguinal ring. In the monolocular variety (fig. 4), the interstitial sac is a direct continuation of the inguinal hernia and not a diverticulum with an inguinal hernia descending further down the canal. If the ectopic testicle is at the external ring and prevents the further descent of the hernia, the only direction in which the sac can expand is between the layers of the abdominal muscles. As there is no loculus going down into the scrotum, the hernia must of necessity be monolocular. At operation, the enterocele between the muscles is found to be a direct continuation of the sac that comes down the inguinal canal, while the process vaginalis is completely closed and in the majority of cases does not even descend into the malformed, empty scrotum. Goebell was able to collect reports of twenty-four such cases of monolocular interstitial hernias and eighty-four of the bilocular variety. In our series there were ten monolocular, thirty-six bilocular, and twenty-one that could not be diagnosed because of insufficient data.

In another variety of monolocular hernia the interstitial sac lies adjacent to but not communicating with the inguinal canal (fig. 5), and opens into the abdominal cavity through its own orifice, which lies near the internal inguinal ring. Kirchner describes such a case in which the sac does not involve the inguinal canal or the internal inguinal ring, but occurs as a separate and distinct entity. In the two cases which we have reported in this paper, the interstitial sac

was completely outside the inguinal canal, and may be classified as an extra-inguinal hernia of the interstitial variety. Perhaps some writers would consider this group as a form of ventral hernia, but its immediate proximity to the inguinal canal precludes this supposition.
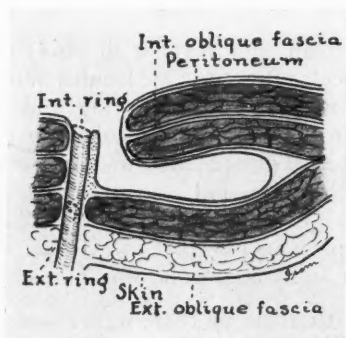

Fig. 5 — The authors' case of interstitial hernia occurring outside the inguinal canal

Etiology.— The same condition that contributes to the formation of properitoneal hernia contributes also to the production of the interstitial variety. The most satisfactory explanation of this form of rupture is based upon its connection with retained testicles. The testicle usually is situated at or just outside of the inguinal ring, and bars the further descent of the hernial sac, causing it to spread between the layers of the abdominal muscles. In Macready's 129 cases of males, abnormalities of the testicles were present in 73.4 per cent, and in 67.1 per cent there were congenital displacements of the testicles. In Goebell's 111 cases of interstitial hernia in males, abnormally placed testicles were present in fifty-seven, or 51.3 per cent. Since 1900, forty-five interstitial hernias in men have been reported, and twenty-five (55.5 per cent) of the patients had ectopic testicles. De Garmo describes two cases in which a tube and an ovary were found in the inguinal canal mechanically obstructing the descent of a congenital hernia. The cases of Macready and Goebell, combined with our series produce a total of 285 cases of interstitial hernia in males, in 186 of which the factor of retained testes was present, making a total of 65 per cent with congenital aberrant testes. Macready states that in practically all hernias of this group there is a maldevelopment of the scrotum which prevents

the normal descent of the testicle and process vaginalis. Moynihan strengthens this belief by showing that the scrotum is never fully occupied by the testicle.

That an ectopic testicle is not the only etiologic factor present, however, is evidenced by the occurrence of interstitial hernia in males with normally placed testicles, and in females. Our series includes the records of twenty-two women in whom interstitial hernias were present.

We believe that the preformed pouches of Rokitansky play a lesser part in the formation of these hernias than in the properitoneal variety; yet how can we explain the existence of the form of interstitial hernia which occurs separately from the inguinal canal unless we accept the premise that it developed in a congenitally preformed sac? The case of Kirchner, together with our two cases, illustrates this form of hernia.

Incidence.— The incidence of interstitial hernia seems to vary, as Langton observed forty-two in 50,000 herniorrhaphies, while Remedi encountered twelve in only 760 such operations. The condition occurs 3.5 times more frequently in men than in women. In Goebell's series of 115 cases, four were in women. Of Macready's 163 interstitial hernias, thirty-four were in females, while Auvray reports fourteen and Berger eight cases in women. Thus far we have been able to find 285 interstitial hernias in men and eighty-two in women. The average age incidence in males was thirty-six and in females fifty-six. The youngest patient reported was four months old and the oldest sixty-six.

Symptoms.— The outstanding clinical syndrome is that of intestinal obstruction, as evidenced by the fact that in Goebell's 115 cases, ninety-seven hernias were incarcerated. In our series thirty were incarcerated, fourteen were reducible, and in twenty-three no history was given. If a patient complains of pain in the inguinal region, is nauseated and vomits, and if examination reveals an ectopic testicle with a palpable mass above Poupart's ligament, the presence of interstitial hernia should be suspected. The intermuscular swelling, however, cannot always be palpated, the testes may be in the scrotum, and the obstructive symptoms may be missing. In such cases the diagnosis is difficult and, in fact, impossible. In our two cases no obstructive symptoms were present. Both patients complained of pain in the inguinal region which was accentuated by straining and was relieved by lying down. No inguinal mass was present. We surmised that we were dealing with some abnormal form of hernia, the exact nature of which we did not know.

SUPERFICIAL HERNIA

Boyer, in 1822, was the first to describe a hernia which proceeded from the external inguinal ring and spread out between the aponeurosis of the external oblique muscle and the integument. He termed it intra-inguinal hernia. In 1886, Le Fort revived interest in this variety of hernia, but it remained for Kuester, in 1887, clearly to describe and to define this rare condition, which he named inguinosuperficial hernia. He presented histories of fourteen cases and discussed the probable etiologic factors concerned in their production. In 1903, Moschowitz collected sixteen cases and added one of his own. In 1905, Sellenings published reports of a series of twenty-seven cases which he had collected. In a review of the literature we have been able to accumulate records of ninety-six cases, some of which date back to 1893 and are not included in any of the aforementioned series. We realize that it is a hopeless task to collect all reported cases because of the variety of titles and subjects under which they have been published. Many reports of so-called superficial inguinal hernias had to be discarded because of insufficient data which made it impossible to determine accurately their anatomical position.

The addition to our series of that of Sellenings produces a total of 123 authentic cases of superficial hernia.

Definition and Anatomical Considerations.— In inguinosuperficial hernia the sac descends into the inguinal canal, then through the external inguinal ring, and spreads out between the aponeurosis of the external oblique muscle and the skin. The sac may occupy one of three positions: (1) It may pass laterally toward the anterosuperior iliac spine. This is the most common location. (2) It may extend upward and medialward toward the umbilicus, as in Broca's case. (3) It may pass downward over Poupart's ligament and come to lie directly over the femoral opening between the deep fascia of the thigh and the skin.

Cases belonging to the last group have often been described as inguinofemoral hernia. In fact, Twyman considers them a clinical entity and reports the cases of Holthouse, Key, and his own as being representative of this variety. It seems to us that these are true inguinosuperficial hernias, and should be so classified. An inguino-femoral hernia, as the name implies, is one involving both inguinal and femoral canals. For example, an inguinal hernia passes down the inguinal canal as far as the lower part of the canal; then because of an anatomical defect it passes beneath Poupart's ligament and emerges through the femoral openings. In Twyman's case the hernial

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sac came through the external inguinal ring, passed downward over Poupart's ligament, and was found in the superficial tissue in Scarpa's area. The hernia was inguinal, and never came into contact with the femoral canal; hence it is merely a superficial inguinal hernia, and should be so classified.

' The bilocular theory of Moynihan again is applicable to this form of hernia, one loculus passing down into the scrotum or labia and the other passing out between the aponeurosis and the integument.
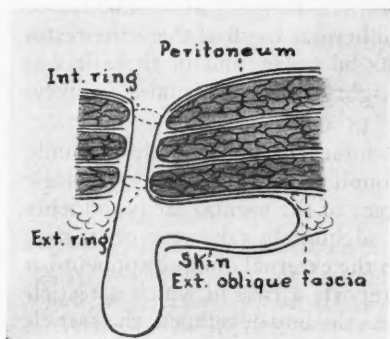
Fig. 6
Bilocular superficial hernia
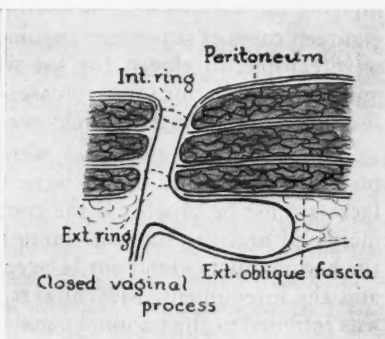
Fig. 7
Monolocular superficial hernia

(fig. 6). It is true that in some cases the superficial hernia is merely a diverticulum from the process vaginalis and that the main portion of the hernia descends into or near the scrotum. On the other hand, we have found cases in which the process vaginalis is situated between the external oblique aponeurosis and the skin, there being no hernial sac descending into the scrotum. When the process vaginalis and the testicle are both ectopic, it seems that they constitute true monolocular hernia. Goebell maintains that the monolocular variety is just as prevalent in the superficial hernias as in the other forms of interparietal hernias which have been discussed so far (fig. 7). In our series of ninety-six cases of superficial hernias thirty were bilocular, ten monolocular, and in fifty-six insufficient data made it impossible to determine the nature of the interstitial sac.

Etiology.— Practically all that has been said concerning the etiology of properitoneal and interstitial hernia could be mentioned as being causative factors in the formation of superficial hernias. The pathogenesis of this variety of hernia, however, is concerned

chiefly with congenital malformations of the process vaginalis and the testicles. As a rule, both are placed between the skin and the external oblique aponeurosis, and very seldom communicate with the scrotum. In those few cases in which the process vaginalis and the testicle enter the scrotum, the superficial hernia is merely a diverticulum from the walls of the scrotal hernia. In other cases the testicle is ectopic, but the vaginal process enters the scrotum, although it is completely obliterated below the testicle. The spermatic cord usually is short, and Schmidt considers this a factor in inhibiting the normal descent of the testicle. In 1900, Goebell collected eighteen cases of superficial inguinal hernia. In all of these the testes were ectopic, in eleven the sac was bilocular, and in three it was monolocular. In our series of cases eighty-six were in males, in sixty-seven of whom ectopic testicles were present.

However, as eight cases were found in males with normally placed testicles and seven were found in females, other etiologic factors must be sought. If the content of the hernial sac is suddenly increased and the scrotum cannot adequately take care of it, then the hernia must extend out between the external oblique aponeurosis and the integument. Moschowitz reports a case in which a testicle was retained in the inguinal canal. As the boy developed, the testicle gradually descended into the scrotum, but since the descent was accompanied by pain, he frequently forced the testicle and the accompanying congenital hernia back out of the scrotum. Following such a reduction, the testicle and hernia were forced out between the external oblique aponeurosis and the skin, as the external inguinal ring was too small to permit their return into the inguinal canal and abdomen. The hernia became strangulated, and at operation the sac was found to be as described. Repeated and indiscriminate taxis, therefore, may produce this form of hernia.

Incidence.— The incidence of this group is very low. So far, only 123 cases have been described, 101 in males and seven in females, and in fifteen the sex was not mentioned. The average age is forty-five years.

Symptoms.— The symptoms of superficial hernia usually are those of intestinal obstruction. Out of ninety-six cases, thirty were irreducible and presented symptoms of obstruction, twelve were reducible, and in fifty-four no clinical history was given. In this type, a palpable tumor generally is encountered about Poupart's ligament, and when the scrotum is examined the testicle is missing. It must be remembered, however, that in a few cases the superficial sac may pass downward into the region of the femoral ring and be mistaken for a femoral hernia.

Treatment of Interparietal Hernia

As most interparietal hernias are either incarcerated or strangulated when the patient presents himself, immediate operative intervention is indicated. Delay merely increases the risk of mortality. If a patient presents symptoms of intestinal obstruction following an inguinal or femoral herniorrhaphy, an incarcerated properitoneal hernia should be suspected, and intervention should be instituted immediately. In all herniotomies, in order to be certain that an intermuscular sac has not been missed, the entire inguinal canal should be carefully explored. When operating on an interparietal hernia, the surgeon must remember that the strangulation may be at the internal ring, the neck of the interstitial diverticulum or sac, or the external ring. The abdomen never should be closed until the site of obstruction has been found. Generally, careful exploration will reveal the enterocele in a diverticulum.

In an operation for interparietal henia, some surgeons prefer the inguinal approach, and then, if necessary, the incision can be extended until the abdomen is opened. Moynihan thinks that a combined abdomino-inguinal route is better. It seems to us that the latter is the more practical, as it precludes injury to the bowel, since the site of obstruction is more clearly revealed by this approach.

In dealing with simple non-strangulated hernias, all that is necessary is to isolate the sac, ligate it, and close the hernial tract through the abdominal parietes.

Summary

1. Interparietal hernia is a term used to designate a group of hernias which occur in the inguinal region between the various layers of the abdominal muscles, and are classified according to the anatomical location of the hernial sac.

2. Properitoneal hernia includes all those cases in which the hernial sac lies between the peritoneum and the transversalis fascia, 119 such cases being reported.

3. In interstitial hernia the sac lies between the transversalis fascia and muscle, between the transversalis and internal oblique muscles, or between the two oblique muscles, 348 such hernias having been reported.

4. In superficial hernia the sac lies between the skin and the aponeurosis of the external oblique muscle. We have found 123 cases of this type.

5. In interparietal hernia the sac may be monolocular or multi-locular, the latter being the form present in the majority of cases.

6. The usual clinical picture is that of intestinal obstruction.

7. Treatment consists of early recognition and immediate relief by operation.

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TUMOR OF THE SPINAL CORD ASSOCIATED WITH BILATERAL ACOUSTIC TUMORS

Report of a Case

W. James Gardner

The patient, a report of whose case follows, is a member of a family in which bilateral deafness has been transmitted as a true mendelian dominant character. The condition has been traced through five generations of the family, which includes 217 members.[1] Thirty-eight members have been affected. Of these thirty-eight, fifteen subsequently became blind, the blindness being preceded by headache and vomiting in each case in which information was available. Of the deaf and blind persons, four were examined prior to death, and were found to have choking of the optic disks with secondary atrophy. Of the deaf persons, seven were personally examined. Five of these had entire absence of vestibular responses in the Barany test. In the other two, a sluggish response was obtained from the left horizontal canal, but the remaining semicircular canals were nonfunctioning. In addition, four subjects were found who had little or no impairment of hearing, but whose vestibular responses were absent in the Barany test. These Barany observations, together with the neurologic signs which these persons presented, made the diagnosis of bilateral acoustic tumors practically indisputable. The two affected members of this family who came to necropsy had bilateral acoustic neurofibromas. There was practically no associated evidence of von Recklinghausen's disease in this family, and at the time of the investigation, there was nothing to indicate the presence of tumors elsewhere than on the acoustic nerves.

Following publication of the first report on this family, however, one of the affected members, the subject of the following case history, developed symptoms of a tumor of the spinal cord. The tumor, which proved likewise to be a neuro-fibroma, was correctly localized and successfully removed. Therefore, it seems probable that other affected members of this family may also have tumors on other portions of the central nervous system.

1 Gardner, W. J., and Frazier, C. H.: Bilateral Acoustic Neurofibromas; A Clinical Study of Field Survey of a Family of Five Generations with Bilateral Deafness in Thirty-eight Members, Arch. Neurol. and Psychiat. 23:266 (Feb.) 1930.

Report of Case

Clinical History. — VA⁹ (fig. 1), a man, was admitted to the neurological service of the Cleveland Clinic Hospital on January 22, 1930, having been referred by Dr. T. K. Wood, of Muncy, Pa. The chief complaint was weakness of both legs and of the left hand.

Fig. 1 — Chart of the patient's family tree. This chart includes only the children of affected parents who attained the age of 20 years, at which average time the condition became manifest. For the sake of simplicity, the charts representing the complete family tree have been omitted. These may be seen by consulting the original article (Arch. Neurol. and Psychiat. 23:266, February, 1930).

The patient who is the subject for this report is indicated as VA9.

The patient had been a little unsteady on his feet, especially after dark, for a period of four or five years. For about two years there had been occasional indefinite cramps in the left hand. For over a year there had been bilateral tinnitus, marked on the left side. For

nine months the patient had noticed some difficulty in retaining feces, and constipation requiring catharsis had been present. For four months there had been progressive weakness and atrophy of the muscles of the left hand and also progressive weakness of both legs. Pain had not been a symptom.

Physical Examination.— The patient was a large, healthy-looking man. His gait was ataxic and lurching, and he tired readily on walking. There were no other points of interest in the physical examination.

Neurologic Examination.— The positive signs were: The retinal veins were slightly engorged, but the optic disks were not choked. A fine horizontal nystagmus appeared on lateral rotation of the eyes. There was a slight impairment of hearing for high tones in the left
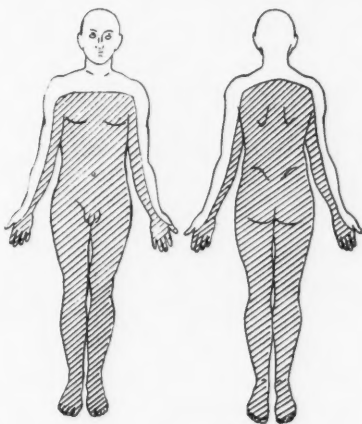
Fig. 2 — Preoperative level impaired for tactile, pain and thermal perception

ear. The lower extremities were weak and spastic. The grasp of the right hand was slightly weak, and the left was extremely weak and flaccid. The dynamometer readings were: right 80, left 5. There was distinct atrophy of the interossei and hypothenar muscles of the left hand and a lesser degree of atrophy in the flexors and extensors in the forearm.

The right biceps and triceps reflexes were normal; the left were slightly exaggerated. The right patellar reflex was normal, but the left was decidedly hyperactive. On testing the achilles reflexes, a bilateral ankle clonus was elicited. The Babinski response was positive on both sides. The corneal reflexes were normal. The abdominal

and cremasteric reflexes were absent. The Romberg sign was strong-
ly positive. There was no dysmetria in the finger-to-nose or heel-to-
knee tests. There was decided impairment of tactile, pain and
thermal perception up to and including the eighth cervical segment
(fig. 2). It was not possible to demonstrate a pilomotor or vaso-
motor level. Horner's syndrome was not present.

Diagnosis.— On the basis of the atrophy of the muscles of the
left hand, the sensory level and the freedom from pain, the diagnosis
was neurofibroma of the left eighth cervical anterior root.

Vestibular Studies.— Tests by Dr. W. V. Mullin disclosed that
the right labyrinth was entirely nonfunctioning, while a very slug-
gish response was obtainable from only the horizontal canal on the
left side.[2] The hearing was normal with the right ear, but there was
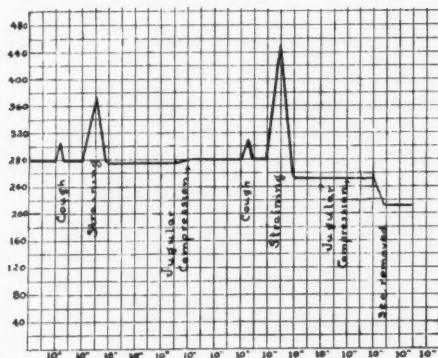
Fig. 3 — Graph of the spinal fluid pressure responses, indicating practically a
complete block on jugular compression and a partial block on straining.

a mild nerve deafness on the left. These observations, together with
the family history, indicated the presence of bilateral acoustic
tumors.

Spinal Fluid Examination.— At the spinal puncture, the initial
pressure was found to be 280 mm. of water (fig. 3). The pressure
rose to 295 when the patient coughed, and returned promptly to
280. Straining increased the pressure to 365, and it fell to 275 on
release. Jugular compression for ten seconds caused a rise only to
280. On straining once more, the pressure rose to 445, and fell
promptly to 250. Jugular compression was again applied for ten
seconds, with no response. The withdrawal of 3 cc. of fluid reduced

2 Similar results had been obtained by Dr. James A. Babbitt and Dr. Lewis
Fisher, of Philadelphia, a year previously.

Fig. 4 — Roentgenogram made after the introduction of 2 cc. of campiodol into the lumbar sac. The lower border of an oval tumor is outlined.

the pressure to 210 mm. of water. The jugular-compression tests indicated a complete block from above downward, but the response to straining indicated that the block was not complete from below upward, as the pressure after straining was found to be below the initial pressure.[3] A specimen of the fluid was faintly yellow. It contained 5 cells per cubic millimeter and the globulin was four plus. The Wassermann and colloidal gold reactions were negative.

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3 The latter point is of interest and can be demonstrated in many cases of partial block. It has not received mention in the literature.

In an effort to exclude the presence of other spinal tumors below the level of the main lesion, an injection of iodized oil was performed in the lumbar region. Roentgenograms taken with the patient in the head-down position showed that the oil stopped at a point opposite the middle of the body of the first dorsal vertebra, where it outlined the lower border of an oval tumor (fig. 4). No evidence of obstruction of the oil elsewhere was manifest. Operation was decided on, therefore.

Operation.— A laminectomy was performed, the laminae of the third cervical to the first dorsal vertebrae, inclusive, being removed. On opening the dura, the arachnoid membrane was found to be non-pulsating except at the extreme upper end of the exposure. In the upper two-thirds of the exposure, the cord was displaced backward and flattened as though by a tumor on its anterior aspect.
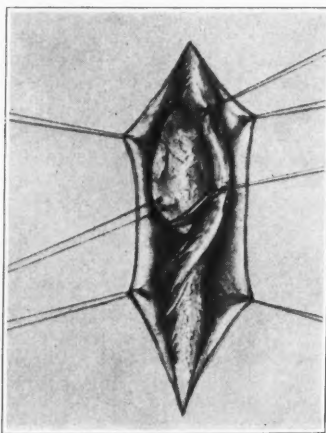
Fig. 5 — The tumor in situ after it had been freed from its distal attachment to the left eighth anterior cervical root.

The eighth cervical and first thoracic posterior roots were sectioned on the left side, after which the cord was gently rotated and pulled to the right. This disclosed a yellowish-pink, smooth, firm tumor anterior to the cord. The tumor was firmly adherent where the left eighth cervical root made its exit from the dural sac (fig. 5). The tumor was freed at this point with a scalpel and removed from the canal. The left eighth cervical anterior root was found to be thickened and elongated up to the point at which it made its entrance into the tumor. About 2 cm. of the proximal portion of this root was removed with the tumor. The point of attachment of the tumor to

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the distal portion of the root was then thoroughly curetted and painted with Zenker's solution. The cord was replaced in its normal position in the canal and the wound was closed. Aside from a minor wound complication, the patient's convalescence was uneventful.

Course.— One month after the operation, a neurologic examination showed the following: The gait was slightly ataxic and the
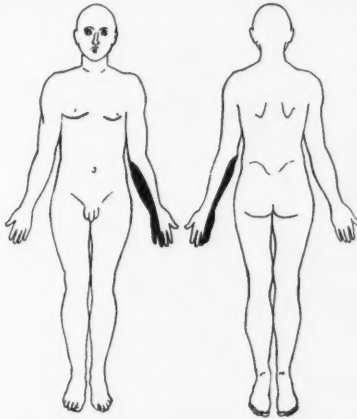
Fig. 6 — Postoperative anesthesia resulting from operative section of the eighth cervical and first thoracic posterior roots.

Romberg test was mildly positive. Nystagmus was present as before the operation. The biceps, triceps and achilles reflexes were normal. The left patellar reflex was moderately exaggerated; the right was normal. The Babinski response was negative, and there was no

Fig. 7 — Photograph of the tumor after its removal, showing the point of entrance of the nerve. Its point of exit is marked by the abraded area in the capsule.

ankle clonus. There was a slight improvement in the strength of the left hand, but the atrophy was unchanged. There was complete anesthesia on the ulnar side of the left forearm and hand (fig. 6).

Pathologic Report.— Grossly, the specimen consisted of an oblong, flattened, encapsulated tumor, removed from the anterior root of the left eighth cervical nerve (fig. 7). The proximal portion
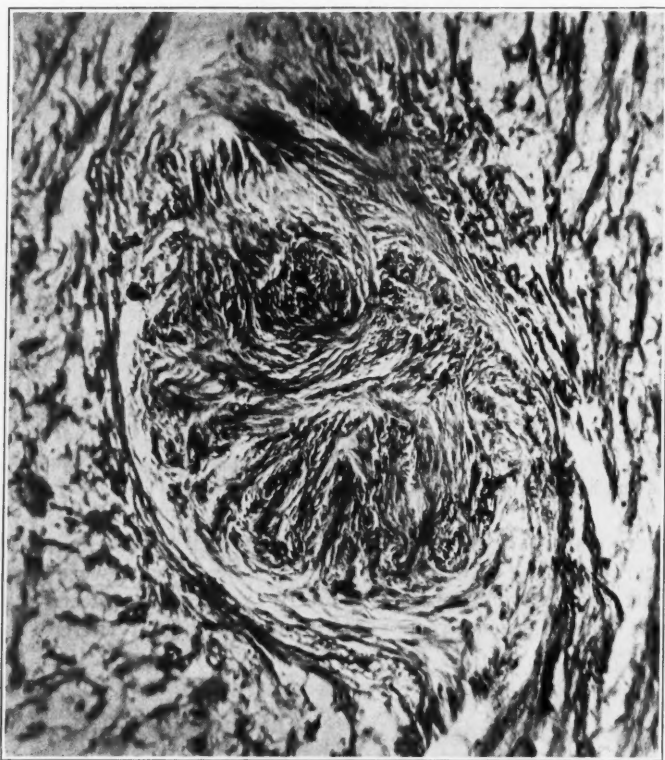
Fig. 8 — Photomicrograph showing the typical structure of a neurofibroma. Hematoxylin and eosin stain; X 125.

of the anterior root was present, measuring 1.5 cm. in length and 0.5 cm. in diameter. It was grayish in color, moderately soft, and appeared edematous. Distally, the anterior root expanded into a tumor, which was flattened and roughly oval in shape, measuring 3.2 by 2.2 by 1.3 cm., and weighing 8 gm. Directly opposite the anterior root was an abraded area marking the point where its

fibers continued distally to join the dorsal root. The remainder of the tumor was covered by a thin membrane containing numerous fine blood vessels. The specimen was preserved in Zenker's solution before sectioning (fig. 8).

Microscopically, a section through the nerve showed a mass of tumor tissue made up of bundles of spindle cells running in various directions, with a tendency to form whorls. The nuclei varied con-
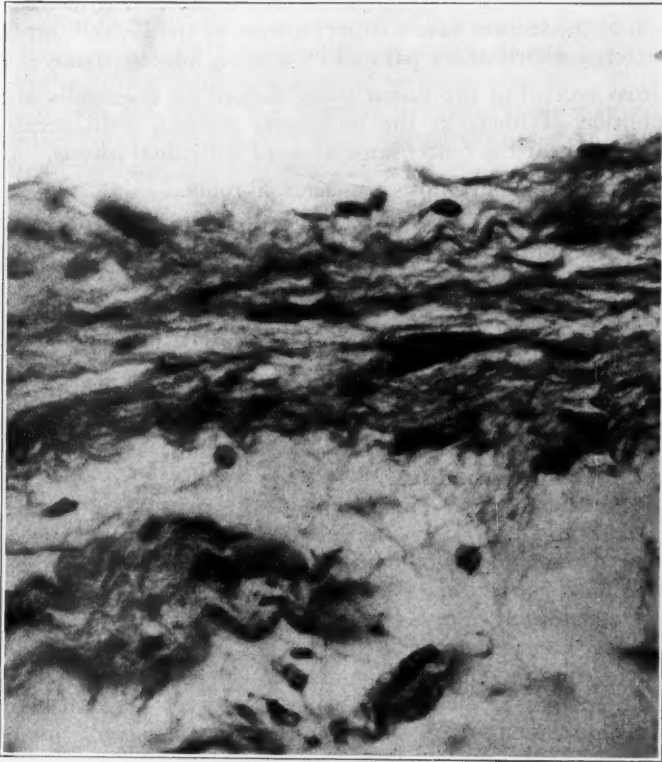
Fig. 9 — Same field as in figure 8; X 600

siderably, generally being elongated, but in many instances they were short, oval, and sometimes large, irregular or stellate forms. There was a large amount of blue-staining intercellular substances, principally fibrillar. Along one surface of the section there were fairly large areas of loosely arranged, pink-staining tissue, suggestive

of nerve fibers with degenerative changes. The tumor mass itself had a well defined capsule along one surface. On the opposite surface, the capsule was not so distinct. No collagen fibers were shown with the van Gieson stain.

A longitudinal section of the tumor, fixed with Zenker's solution, included at one end a portion of nerve trunk which had a structure similar to that seen in the section through the nerve. The remainder of the section consisted of an outer lamellated zone of long, wavy fibers, loosely arranged and with few nuclei present. In the central portion of the section were compact masses of spindle cells arranged in scattered whorls and separated by a loose, fibrillar tissue.

Gross section of the tumor mass showed an essentially similar distribution of fibers in the peripheral portion, with occasional whorls, and near the center large areas of individual whorls.

The pathologic diagnosis was neurofibroma.

THE DUCTLESS GLANDS AS THEY APPERTAIN TO EYE DISEASES AND TO SURGERY

Albert D. Ruedemann

Any one associated with a medical organization that has much to do with people who have endocrine disturbances will be impressed by the large number of such individuals who present ocular changes. In the study of these cases it becomes of increasing interest to find that these pathologic changes in the eyes not only can but must be due to the deficiencies of the internal secreting glands.

In only a few cases is it possible to identify one gland as responsible for the ocular condition, for usually more than one is causing trouble. Until better methods of study of the endocrine glands are introduced, and better surgical operations are performed on those which are at fault, disorders of the thyroid and of the pituitary will continue to be considered as the principal causes of diseases of the eye which are amenable to surgery.

In this connection, I wish to record the recent work of Dr. G. W. Crile on the suprarenals. There is a group of cases, the symptoms of which simulate those of hyperthyroidism, in which the condition is frequently called neurasthenia or neurocirculatory asthenia. In these cases the eyes may present all the changes that are associated with hyperthyroidism except exophthalmos. Such cases appear to be benefited by the denervation of the suprarenals. (As a matter of interest, it may be mentioned that studies of the ocular tension in these cases have not as yet revealed any constant rise or fall in intra-ocular tension.) These cases must be followed further for we have seen but sixty of them and until we know more about them, a definite report cannot be made. Nevertheless as the result of a careful review of these sixty cases, Dr. J. Lehman reports that the best results were obtained in those in which the symptoms of hyperthyroidism were very closely simulated. These patients have a rapid pulse, widening of the palpebral fissures with no exophthalmos, some weakness of accommodation convergence, tremor on closing the eyes, and no difficulty of eversion of the lids. They do tend to have larger pupils, but no true exophthalmos has been seen. The eye signs all disappear after the suprarenals have been denervated. It must be realized that these patients would not be benefited by a thyroidectomy; as a matter of fact, I believe that it is in such cases that postoperative hypothyroidism develops with the progressive exophthalmos which all too frequently accompanies this condition.

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Everyone has had experience with cases in which diseases of the eyes have been associated with thyroid disturbance and with the effects of thyroid surgery. The following statements regarding this relation are based on my personal records of approximately 1,500 cases of diseases of the thyroid gland, in 1,000 of which the condition of hyperthyroidism was present when the patient was first examined by me. I do not present this, however, as an isolated report of such observations for there have been many well presented reports of such cases. Those of Dr. Holloway and Dr. Murray, of Minnesota, are excellent examples of the large numbers of these cases which exist throughout the country. The literature presents many case reports, most of them, however, made by surgeons few of whom record the eye signs accurately. Unless actual measurements are made, the eye changes cannot be correctly interpreted. Photographs are extremely misleading.

Before beginning a discussion of the diseases of the thyroid gland that are associated with eye changes, it is necessary to identify the clinical group of diseases of the thyroid which I use here. I consider only cases of hyperthyroidism with or without adenomatous changes, for thyroid disease without toxicity as a rule does not produce eye changes.

In this group of cases, retraction of the upper lid is an earlier sign of eye change than is exophthalmos and is present in a higher percentage of cases than exophthalmos. It is frequently unilateral and frequently unequal. The wide retraction of the upper lid is associated with some orbicularis tension which offsets it. This first and most common eye sign accounts for many of the other eye signs — the staring, the difficulty of eversion, the infrequency of winking, the tremor on closing. Secondarily it accounts for the photophobia, because of the complete uncovering of the pupil and the iris; the excessive tears due to exposure, and the associated conjunctivitis catarrhalis thyroiditis. This is the type of case in which a corneal ulcer may develop. Retraction of the upper lid is the eye condition most helped by thyroidectomy — the wide retraction of the lids is almost immediately benefited and with it the appearance of the patient.

Patients belonging to this group of cases with wide retraction of the lids are frequently photographed before and after operation to show the end-results of thyroidectomy in its effect on exophthalmos. However, in but few cases are any actual measurements given.

Widening of the palpebral fissure is an entirely separate eye sign which occurs frequently unaccompanied by exophthalmos. It is

greater, however, when it is associated with protrusion of the eyes. Exophthalmos also occurs separately with little or no widening of the fissures and in some cases with extreme palpebral spasm on one side, while the other fissure may be narrowed in spite of the presence of definite exophthalmos.

Exophthalmos is present only in cases of hyperthyroidism. If there is no toxicity, there is no protrusion of the eye. We have never had a case of unilateral exophthalmos in a case of hyperthyroidism; all cases of unilateral exophthalmos have been cases of pseudo-exophthalmos due to unequal or unilateral retraction of the lid. In a series of 100 cases exophthalmos developed following thyroidec-tomy and in one of these cases extreme unilateral exophthalmos was present for a period of three months accompanied by severe hypo-thyroidism. In another case of postoperative unilateral exophthal-mos a large mucocele was found to be present on roentgen examina-tion.

Thyroid surgery has been found to be of great benefit in cases of exophthalmos. The progress of the protrusion is halted; ulcers are healed, and other eye signs due to exophthalmos show improve-ment. The average amount of decrease of protrusion is between 2 and 3 mm., the amount of protrusion varying slightly in the two eyes — rarely over 2 mm. The degree of protrusion is no indication of the degree of toxicity present and may be as great as 19 mm. over the high normal of 20 mm. which we have established for our series after measuring the protrusion of 1,000 normal eyes. Anterior luxation does not occur when the disease is diagnosed early enough and treated surgically. It may be necessary to operate earlier in the presence of cardiac complication or even in severe disturbances of the nervous system.

That group of cases which is extremely annoying to the surgeon and the ophthalmologist is that in which exophthalmos develops postoperatively. Fortunately, there are not many of these; but, since the exophthalmos progresses slowly, there is a tendency to consider the condition as a recurrence of hyperthyroidism and to perform a second operation whereas these patients already have a deficient thyroid secretion. These are cases of transitory hypo-thyroidism and they present several other features, such as progres-sive lowering of the basal metabolic rate, and edema as seen in the case of myxedema (upper and lower lids); no widening of the lids is present except that which is due to the exophthalmos. These pa-tients do not stare; there is no difficulty of eversion; but there is a great deal of weakness of accommodation convergence. Active treat-

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ment with thyroid extract offers these patients the greatest relief. In our series the group in which exophthalmos developed postoperatively did not have severe eye signs before operation in the form of exophthalmos due to hyperthyroidism but rather in that form which is noted in association with suprarenal dysfunction or polyglandular disturbance. From my observation, this type of patient does not have an extremely high metabolic rate or a very rapid pulse rate but may present all the other signs of hyperthyroidism.

Disturbances in muscle balance and isolated muscle palsies are common in cases of hyperthyroidism, but whether or not these conditions are due to exophthalmos is a question. There are numerous cases of isolated paralysis, such as that of the external rectus muscles and most frequently the right external rectus. The superior recti, especially the right superior rectus, are most frequently involved. The muscle changes do not clear up to any great extent after operation and may require further operative treatment later on. In six cases in which a squint operation had been performed, after a long period of time the eyes were found to be in maximum divergence or convergence, the opposite of the condition for which operation had been performed.

Weakness of accommodation convergence is the most common muscle disturbance and persists postoperatively, frequently delaying the return of the patient to normal and preventing his assuming his previous occupation. Muscle exercises and prisms for close work are sometimes of some benefit for this condition.

In our series of cases of hyperthyroidism there were eleven cases of increased intra-ocular tension, in none of which were any fundus changes of glaucoma present and in none of which were there any field changes or loss of vision. All but one of these patients returned to normal immediately after operation. This one case was that of a woman with myopia with a persistent tension in excess of 30 (Schioetz). The condition was controlled by the use of physostigmine. In all of these cases a great degree of protrusion was present with severe toxicity; all the patient had severe headaches, which also disappeared postoperatively.

In an ever enlarging group of cases of weakness of accommodation convergence, rapid fatigue, increase in body weight and all other symptoms usually associated with a mild postepidemic encephalitis, a low basal metabolism is found ranging from minus 10 to minus 40. These individuals all are benefited by the administration of thyroid extract replacing the nux vomica and other stimulat-

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ing tonics that were formerly used. Disturbances of the eye muscles are commonly associated with general disability, and the possibility that hypo-endocrinism with poor muscle balance is present must always be considered.

With the ever increasing number of thyroidectomies and also the number of severe cases in which surgery is always hazardous though necessary, there may be an involvement of the parathyroid glands — either by their accidental removal or by their involvement in the post-operative scar, or perhaps by the temporary cutting off of their blood supply. There is undoubtedly a group of cases in which tetany is present before operation — those cases in which the patient complains of transitory blurring of vision, or spasm of the ciliary muscle. A large percentage of these patients have refractive errors that have varied several diopters even after a recent examination. Our records show that in over 60 per cent of thyroid cases refractive errors were present for which new glasses had been prescribed three months prior to the necessary surgical operation.

Although routine examination in the following group of cases did not reveal preoperative changes in the lens, postoperatively eye changes occurred as follows: sudden and spasmodic blurring of vision, becoming more frequent in association with some photophobia and then occurring for longer periods and, in some instances, soon accompanied by a haziness of vision. Examination at this time revealed a deposit along the posterior cortex which was granular to flaky in character. This condition progressed and appeared to form spicule-like changes, all posterior, in part as if the lens were thrown in folds. The spasms were of longer duration and lasted from a few minutes to three or four hours. In cases of this type, changes in the lens may progress rapidly to the formation of a complete cataract in one month or they may slowly progress over a period of several years. In all our cases, surgery had to be instituted because the condition was bilateral and because it was necessary in order to save the patient's vision. These patients had low blood content of calcium and an increase of phosphorus, and other signs of parathyroid disturbance.

Just a word of warning in regard to eye surgery in these cases — the condition of the patient must be known before any operation is undertaken. The calcium report should be in the surgeon's hand before he operates; otherwise, he will have to contend with the most severe convulsive type of vomiting. This condition may be controlled by the administration of intravenous injections of 10 cc. of calcium chloride in 5 per cent solution, some sodium chloride

being used before and after the administration of the calcium chloride to make sure that it flows easily and that it is washed in afterward. Dr. McCullagh, who has had these patients under observation, states that his best results have been obtained by the administration of two heaping teaspoonfuls of calcium lactate as often as every two hours, the dose being decreased as the blood calcium increased. He has found it unnecessary to use any other forms of calcium.

With this knowledge of the patient's condition, the surgical risk of thyroidectomy in these is the same as in other cases. In our own series of nine operations, good results were secured in seven; in two, good visual results were obtained in spite of iris prolapse. In both of these cases, severe vomiting occurred shortly after operation. All our patients were women under 50 years of age except two, one of whom was 52, the other 60. In all the cases in which cataracts formed, the condition developed directly after thyroidectomy. The question arises whether the cataracts are due to spasm or to low calcium content. These patients must be kept under medical observation and an attempt must be made to transplant parathyroids, although to date in cases in which this procedure has been attempted satisfactory results have not been secured. In 150 cases of deficient parathyroid secretion, cataract has been present in 10 cases, or 7 per cent.

Eye disorders are probably an involvement of disturbances of the pituitary gland as often as of disturbances of the thyroid gland, but on account of the inaccessability of the former the lack of proper methods of examination makes it difficult to find out whether this gland is responsible for the eye condition.

In a group of children with progressive myopia but otherwise normal, we found a very low dextrose tolerance curve and a low basal metabolic rate. We do not believe that enough time has elapsed for a complete report to be made of these cases. There is some constant factor in the production of the high degree of myopia and of hyperopia of the corneal disturbances, which range from high astigmatism to irregularities and keratoconus. These cases belong in the hypopolyglandular group. We have found two cases that were exceptions to this rule — both in women. In one, marked corneal irregularity was present. This patient had suffered from severe hyperthyroidism; her basal metabolic rate had fallen from plus 86 to minus 40. This condition was associated with a general glandular dysfunction. The other patient, in whom marked keratoconus was present, was in the hyperglandular state although she did not present a typical case of hyperthyroidism.

In a family of five boys, whose father and mother were second cousins, four of these boys (ages varying from 5 to 11 years) were blind. They were affected by hypopituitarism. In two of these cases the low basal metabolic rate indicated the presence of hypothyroidism. The blindness was due to a granule-like pigmentary degeneration of the retina (not a retinitis pigmentosa type). In two other cases, in both of which pituitary disturbances were noted, similar granular degeneration was present. These changes were more marked well out in the periphery.

The difficulty in the study of the endocrine glands has been the lack of accurate measurements, the passive interest of the general practitioner and the too aggressive interest of the endocrinologist.

CONCLUSIONS

The following facts are noteworthy:

1. Frequently it is found that patients who are examined for glasses have a muscle imbalance which may be due to hypothyroidism or other glandular dysfunction.

2. Hyperthyroidism produces definite eye changes, which in most cases are benefited by surgery; namely, wide fissures, ulcers and exophthalmos. Associated muscle changes are little benefited by any treatment, medical or surgical.

3. In parathyroid tetany, lens changes are sometimes present, probably the result of a combination of spasm with a deficiency of calcium and an increase in phosphorus.

4. Dysfunction of the pituitary gland is a causative factor in certain retinal disturbances and is an associated factor in other eye changes probably of polyglandular origin.

5. The recent work of Dr. Crile also brings out a group of cases in which suprarenal dysfunction is associated with eye changes.

AN ANALYSIS OF 1347 CASES OF MALIGNANT TUMORS OF THE BREAST WITH SPECIAL REFERENCE TO MANAGEMENT AND END-RESULTS

GEORGE CRILE

The one important point to bear in mind in the consideration of any tumor of the breast is that it may be the starting point of a malignant growth. This is true whatever etiological factors may seem to have been involved in the formation of the tumor; whatever its site, whatever the age of the patient, whatever the family history may disclose. We shall have more to say regarding the potentialities of each of these factors; we mention them here only for the purpose of once again sounding the tocsin for though it has been sounded persistently by many writers on this subject, still the warning has not been sufficient for a period of watchful waiting is allowed in too many cases of apparently benign growths with dire results to the patient.

Age Incidence.— The greatest incidence of cancer of the breast is generally placed in the decade between 46 and 56 years. So often has this statement been made that there is danger of overlooking the fact that cancer of the breast may occur at any age. In our own series of cases the range has been from 20 to 87 years (table 1).

TABLE I
Age Incidence of Malignant Tumors of the Breast
(Cleveland Clinic Series)

No. of Years	No. of Cases	Per Cent
21-30	18	1.6
31-40	154	13.6
41-50	351	31.
51-60	330	29.2
61-70	211	18.7
71-80	60	5.3
Above 80	7	0.6
Number of cases in which age was stated	1,131	....

I know of no case in which cancer has occurred before the advent of puberty. That cancer of the breast, however, is not entirely dependent upon the changes in the breast due to its functional capacity is shown by the fact that it may occur in man. Wainwright has collected 418 such cases. In our series there have been nine cases of cancer of the breast in man, four of sarcoma and one of Paget's disease.

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In the report of the Metropolitan Life Insurance Company for the years 1911 to 1922 the following statement is made regarding the age incidence of cancer of the breast:

"Cancers of the breast are almost never seen in childhood and very rarely in adolescence. They begin to assume a little importance in the age group of 25 to 34 years. Between 35 and 45 a particularly sharp rise occurs. Among white females of this age group breast cancers become as important as those of the stomach and liver, and the death rate is exceeded by no form of cancer except growths of the genital organs. Among the colored women at these ages, deaths from breast cancers are more numerous even than those from gastric and hepatic growths, and again are exceeded only by those of the genital organs. At ages 45 to 54 the mortality of breast cancers still exceeds that for those of the peritoneum, intestines and rectum, but is not so high as from malignant tumors of the stomach and liver and female genitals. From 45 years upward the rate continues to rise and reaches the maximum for both white and colored women at the highest age group. It is well after the menopause that the hazard from breast cancer becomes greatest."

Heredity.— Since one in ten women after the age of 40 dies of cancer, it is clear that as far as chance is concerned, a cancer history is almost to be expected. Nevertheless, there are families in which the presence of cancer in two or more successive generations raises the question as to whether or not it is hereditary. In our series 257 cases or 28.9 per cent gave a positive history of the occurrence of cancer of the breast in other members of the family. In this connection it is of interest to cite a statement by Johnson and Lawrence:

"Among 500 consecutive cases of carcinoma of the breast treated in University College Hospital, there was a family history of malignant disease in 81, and in 37 of the 81 cases the disease was stated to have been in the breast. In one of this series of cases the patient's mother and her sister died from cancer of the breast and the father's sister from cancer of the mouth; of the patient's sisters two died from cancer, one of the stomach and one of the breast. If heredity plays any important part in the causation of the disease it might be expected that it would lead to its incidence before the average age. In this connection it may be stated that among the 500 cases of cancer of the breast referred to above, the average age at which the disease was first noticed was 49.62 years, whereas among the 81 cases in which any evidence of heredity could be traced, the average age was 48.74 years. The difference in this series of cases is so small as to be negligible but individual cases of carcinoma occurring at an unusually early age are sometimes met

with, as in one of the families mentioned above, in which the probable effect of heredity can not be disregarded."

As a practical clinical matter, it is evident that the hereditary factor in cancer, even if it exists, is not of much importance. Certainly the possibility of hereditary influence should never be even suggested to the daughter of a mother who has died from cancer of the breast.

Trauma.— To what extent trauma predisposes to cancer is uncertain. Nevertheless, that a definite relation may exist between cancer of the breast and trauma is indicated by various published statistics such as those of Hoffman who states that in one series of 314 cases of cancer of the breast trauma was considered as the probable etiological factor in 44 or 14 per cent. In our series there was a definite history of traumatism in only 195 cases or 14.5 per cent. A further suggestion as to the possible influence of traumatism is found in the fact that the most common location of a cancer of the breast is at the point of greatest strain from the weight of the breast. In our series the upper outer quadrant was the site of cancer in 275 cases or 20.4 per cent. One could well imagine the repeated physical injury to which tubules and acini may be subjected by being pressed upon or twisted by the weight of the breast. It would appear that even if there is no causative relation between cancer and *external* trauma of the breast there may be a definite relation between cancer and continual *internal* trauma.

In view of this possible relationship also, massage of the breast is contraindicated. Only the gentlest manipulations should be used, for once cancer has developed massage will promote its dissemination.

In our series 48 cases gave a history of massage of the breast.

Lactation.— Whether or not cancer of the breast bears any relation to lactation has been disputed. Hoffman states that in Ceylon "cancer of the breast is rare though native women suckle their children for a long time." In our series 576 patients had borne children and there is a positive history of lactation in 241 cases.

Precancerous Lesions.— The one important point to bear in mind in considering precancerous lesions of the breast is that almost any lesion of the breast may be transformed into a malignant growth though this occurs but rarely. Nevertheless there are certain lesions of the breast which may safely be exempted from the above generalization. There are simple cysts, lipomata, traumatic fat necrosis, hypertrophy, acute mastitis, mastitis neonatorum, mastitis adolescentium, echinococcus cysts, and syphilis.

Chronic mastitis deserves special consideration because of the diversity of opinion as to its cancerous potentialities. In general it is acknowledged that a lesion of this type may become malignant, especially if the lesion is unilateral. If the condition is present in both breasts malignant changes almost never develop.

Diagnosis.— Unless a precancerous condition has been present in the breast there are no demonstrable symptoms or signs of cancer in its earliest stages. Pain is practically never present in the earliest stages of the development of a cancer anywhere. In the late stages, however, pain may become a distressing symptom.

As Bunts has stated, "axillary involvement, fixation of the tumor, bleeding from the nipple, retraction of the nipple, ulceration of the skin and cachexia are sometimes referred to as the *classical symptoms* of breast cancer. It would be better to discard this classification entirely, however, for if one waits for the development of these classical symptoms the last chance of surgical relief will have passed."

What about biopsy as a diagnostic measure? In our opinion it is never justified, for while it has not been clearly proven, it is highly probable that cutting into cancer tissue may disseminate the disease. If there is even a chance that this may occur biopsy is not justified. In addition, we have found that the scar tends to add further growth energy to a tissue in which an abnormal degree of such energy has already been manifested by the presence of a tumor. Thus it is safer always to remove the tumor in its entirety rather than to cut into it. If this cannot be done without the removal of the entire breast, then the entire breast should be removed. If the tumor is found to be malignant the radical operation may then be completed.

Prognosis.— The prognosis is affected by the stage of the growth, the extent of involvement, the age of the patient, her temperament and personality, the presence or absence of pregnancy and lactation, and the presence or absence of involvement of the axillary glands.

The younger the patient the less favorable the prognosis; the older the patient the more favorable the prognosis. In the eighties and nineties cancer makes slow headway and sometimes seems to grow old and feeble with the patient. Regardless of age, if a cancer is present in an individual with a vivacious, vivid personality, the prognosis is bad. The more nearly the patient resembles a smoked herring the better the prognosis. Cancer in a lactating breast usually develops rapidly and the outcome is usually fatal. As a tragic illustration of the last two points may be offered the case of a patient, with a vivid and vivacious personality, twenty years of

age, who shortly before I saw her had given birth to her first baby. Her breasts were large and turgid. There was a small lump in the upper outer quadrant which was excised and found to be a cancer. A radical excision of the breast with the axillary glands did not even halt the downward course of the patient. The lungs rapidly became involved and death ensued within a few months.

When the axillary glands are involved, especially if many glands are involved, even though they be small, low resistance to the growth or a high degree of growth energy or both is indicated and the prognosis is correspondingly bad. On the other hand if but a single large axillary gland is involved, the prognosis is correspondingly better.

The general prognosis in patients who now present themselves to the surgeon as compared with the prognosis in former years is progressively better. This is the result of the extending propaganda for an immediate visit to the physician when any abnormality in the breast is noted. Patients are now reporting more promptly and the results of operation are correspondingly improved. (table II.)

TABLE II

Length of Time Between Discovery of Tumor and Operation

*No. of cases in which
data are available*

Under 1 month	124
1 to 6 months	377
6 months to 1 year	93
1 to 2 years	92
3 to 4 years	81
Over 5 years	10
	777

Operation.— Once the diagnosis of a tumor in the breast is made, operation should not be delayed. As we have stated, if there is any doubt regarding the malignant character of the growth, it will be found in any considerable series of cases that more lives will be saved by the removal of the entire breast, the axillary dissection being deferred until the immediate report from the pathologist determines the necessity for it.

There is only one condition under which a local excision may be made with entire safety, that is in the case of a single simple retention cyst. It must never be forgotten that the development of carcinoma may be favored by scar tissue. A lump may be removed which is pronounced by the pathologist to be benign. Later, however,

a recurrence may develop in the scar and become malignant presumably as the result of irritation by the scar tissue.

Various incisions for radical operation have been advocated, the best known being those of Halsted, Jackson, Willy Meyer and Rodman. It makes little difference what plan is followed as long as full opportunity for the complete removal is provided with ready access to the axilla.

Halsted believed that the pectoral muscles should always be removed. There are many cases of early cancer, however, in which a sharp dissection of all the fascial planes and a complete axillary dissection removes all the lines of cancer extension, and in such cases cures are effected in as high a percentage as by the more mutilating excisions. Each surgeon will make this decision according to his actual experience.

The axillary dissection should be done in such a manner as to allow a clear view of the glands for not a single axillary gland should be left behind.

The axillary glands are most completely removed by sharp dissection in order to avoid any chance of squeezing out contaminated lymph as might happen with blunt dissection. In our series recurrence in the chest wall or axilla is rare. (table III.)

TABLE III

End Results of Operation for Malignant Tumors of the Breast

Total No. of cases	Carcinoma	All other malignant tumors
Cases available for end-result data	523	32
3-5 year survivals..............	284—54.3%	23
5-10 year survivals............	196—37.4%	21
10 year survivals..............	83—15.8%	11

Radiation.— What is the role of radiation in carcinoma of the breast? Our radiotherapy department under Dr. U. V. Portmann and our surgical division are agreed on the following conclusions: Our experience testifies against the use of radiation before operation. A course of radiotherapy takes time — usually at least two weeks. Radiation, of itself alone, cannot entirely cure a carcinoma of th breast as securely as a complete surgical excision following preoperative radiation since some cells probably would not be destroyed by the radiation, and during those two weeks this residual carcinoma would be growing and extending.

As for postoperative radiation, Portmann, by an extensive statistical study of the comparative results of operations for cancer

of the breast with postoperative and without postoperative radiation has convinced us that (1) the average natural duration of life for a patient with carcinoma of the breast is three years; (2) as a result of radical operation about 38 per cent of the cases will be free from the disease for the natural duration of life and the average survival for five years will amount to about 30 per cent; (3) intensive cross-fire postoperative radiation is harmful but as the result of repeated superficial doses at least ten per cent more patients may be expected to survive for five years than among non-radiated cases; (4) gratifying results may be obtained from radiation in some hopelessly advanced cases of carcinoma of the breast.

Portmann's comparative studies from series of cases in the Cleveland Clinic are given in the accompanying tables. (tables IV, V, and VI.)

TABLE IV

Summary of Results of Treatment of Carcinoma of the Breast

Treatment	Total Cases	Traced Cases	Living 3-5 Years	Living 5-10 Years	Living More Than 10 Years
Operation only	741	523	284—54.3%	196—37.5%	83—15.8%
Operation and Radiation	395	275	124—45.1%	72—26.2%	15— 5.4%
Radiation only	43	22	5—22.73%	3—13.6%	0

TABLE V

Cancer of the Breast
(Cleveland Clinic Series)
Prior to 1924

Treatment	No. of Cases	Living Less Than 3 Years	Living 3 to 5 Years	Living 5 or More Years
Surgery alone	345	39.1%	28.1%	23.1%
Post-operative x-ray	92	39.1%	26.0%	35.8%

TABLE VI

Malignant Tumors of the Breast
(Cleveland Clinic Series)
Since 1924

Treatment	No. Cases	Living or Dead With Recurrence in First Post-Operative Year	Recurrences During 1 to 3 Year Period	Living Without Recurrence First Year	Living 1 to 4 Years No Recurrence
Surgery	50	12 24%	18 36%	20 40%	12 24%
Surgery plus x-ray	61	11 18%	13 21.3%	37 61%	18 29.5%

As Wainright has demonstrated, a malignant growth usually involves the entire mammary area which may be infiltrated with multiple tiny malignant areas many of which seem to be entirely independent of the primary tumor. Such areas as these may well be reached by the postoperative radiation. Another important point in a well-planned attack by radiation is that early metastases below and above the clavicle, and in the chain of lymphatics leading down to the chest cavity, may be destroyed. The added security given by

radiation may be achieved by arresting the advance of the disease beyond the scope of other methods of treatment. (table VII.)

TABLE VII

Sites of Recurrence and Metastasis in Carcinoma of the Breast

1. RECURRENCE:

Local......................................	194	37.31%
Skin.......................................	15	2.88%
Chest Wall...........................	18	3.46%
Axilla.....................................	61	11.73%
Supraclavicular...................	41	7.88%
Other Breast........................	65	12.50%
Other Axilla.........................	17	3.27%
Other Supraclavicular...........	5	0.96%

2. DISTANT METASTASIS:

Abdomen........................		14	2.69%
Abdominal Wall.................		2	0.38%
Bones.............................		79	15.19%
Breast Bone.............	2		
Clavicle..................	4		
Femur....................	11		
Humerus.................	3		
Hip......................	9		
Leg......................	1		
Pelvis...................	14		
Ribs.....................	6		
Scapula..................	2		
Shoulder.................	2		
Skull....................	4		
Spine....................	48		
Sternum..................	3		
Tibia....................	1		
Thorax...................	2		
Carcinomatosis....................		17	3.27%
Cerebrum.........................		10	2.69%
Chest Wall........................		25	4.81%
Esophagus.........................		1	0.19%
Eye...............................		1	0.19%
Gall Bladder......................		1	0.19%
Glands (not including axillary and supraclavicular).................		39	7.50%
Intestines........................		6	1.15%
Kidney............................		3	0.57%
Liver.............................		34	6.53%
Lungs.............................		97	18.65%
Mediastinum......................		15	2.88%
Multiple Metastasis..............		5	0.96%
Ovary.............................		1	0.19%
Pelvis............................		2	0.38%
Stomach..........................		9	1.73%
Scalp.............................		1	0.19%
Total Cases with Recurrence and Metastasis.....			520

Cause of Death.— What is the usual cause of death after operation for carcinoma of the breast? If the radical operation has been performed and postoperative radiation has been employed, the usual cause of death is metastasis in the lungs, and less frequently though not uncommonly in the bony skeleton. When one remembers the rich lymphatic supply of the breast as well as of the tissue planes extending from it, the possibility of early and distant as well as near dissemination becomes manifest.

Statistics.— Our total series of cases of cancer of the breast includes 741 which have been treated by surgery only, 43 by radiation only, 395 by both surgery and radiation.

SUMMARY

1. In the presence of any tumor of the breast during the cancer age its surgical removal should be considered and with few exceptions it should be removed at the earliest possible moment after its discovery.

2. Removal of a tumor of the breast should include the entire breast tissue except in the case of a single retention cyst.

3. Because of the chance of disseminating malignant cells, biopsy should never be performed.

4. The type and extent of the excision should vary with the position and the extent of the cancer — experience and judgment are better guides than any single rule.

5. Postoperative radiation should be employed.

THE FILAMENT-NONFILAMENT COUNT

ITS DIAGNOSTIC AND PROGNOSTIC VALUE

William V. Mullin and Gordon C. Large

Since the time of Ehrlich's epoch-making discovery of a satisfactory method of staining the white blood cells, definite and steady advances have been made in the methods and interpretations of total white blood counts and differential smears. As is well known, the white blood cells were first divided into three types — granulocytes, lymphocytes and large mononuclears. The granulocytes have been further divided into polymorphonuclear basophils, polymorphonuclear eosinophils and polymorphonuclear neutrophils. It is with the latter group that this paper is concerned chiefly.

For many years, differential counts and total counts of the white blood cells have been used as an aid in securing the clinical picture of a disease, the total number of cells and the distribution of types being used mainly as an index of the type of disease present, and the degree of its severity.

In many instances, however, the question in the physician's or surgeon's mind is how to explain certain incompatibilities which arise between the total leukocyte count, the differential smear, and the clinical observations in the case in question.

A distinct advance was made in 1904 and 1905 by Arneth,[1] working at the Leube clinic, when he studied the changes in the nuclear structure of the neutrophils during acute infections. He made a primary division of the polymorphonuclear neutrophils into five classes, each class being recognized by the number of segmentations to the nuclei, the fifth class including those containing five or more distinct segments. He further subdivided these and also the lymphocytes and monocytes until he had in all eighty-one subdivisions.

This was a rather complicated picture, to say the least, as far as being of practical value in making a differential count, but it gave a lead as to the changes occurring in these cells in infections, and a possible explanation of these changes.

In his study Arneth observed that normally the predominating type of polymorphonuclears in the blood stream consisted of those which contain two or more segments, from 90 to 95 per cent being of this class. He showed that the class I polymorphonuclear neutrophil containing an unsegmented nucleus is a young or immature cell
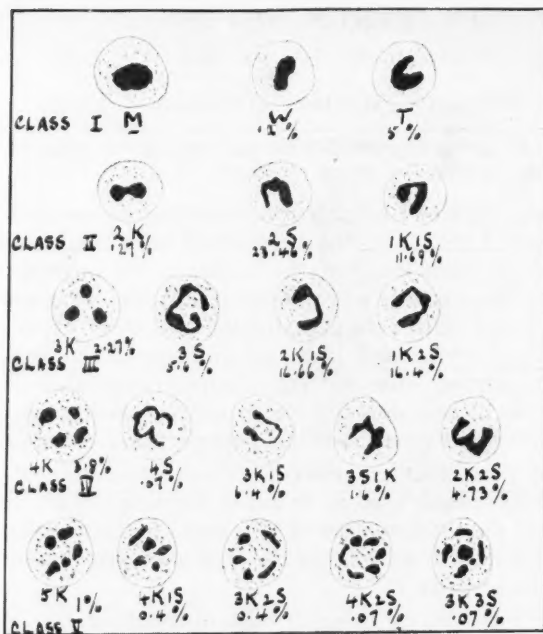
Fig. 1 — Classifications of polymorphonuclear neutrophils by Arneth. From Cooke and Ponder: The Polynuclear Count.

and that the age of the cell is decided by the extent of the segmentation. Arneth pointed out that in acute infection these immature cells increase in number, while the older cells show a corresponding decrease. This change he termed a "shift to the left," and a return from such a change was termed "a shift to the right." These changes are fairly constant, varying with the severity of the infection, the number of immature forms becoming more numerous as the infection grows worse and lessening in number on recovery and convalescence with reversion to the two to five segmented variety.

This appearance of immature forms in the blood stream is explained by a destruction of the normal balance between leukocytic regeneration and degeneration, which is constantly going on in the body. The presence of a leukopenia or a leukocytosis is caused by an inhibition or a stimulation, respectively, of the bone marrow by the bacterial toxin. When increased destruction of white cells occurs in infection, an increasing demand is put on the bone marrow, which is unable to cope with the increasing demand for mature cells and therefore immature cells are poured out.

Although Arneth's observations promoted great interest through-out the scientific world and it was recognized that his procedure was of definite value, it did not come into popular laboratory use because of its complexity and the length of time it took to do one count.

Fig. 2 — Classification of von Schilling, dividing Arneth's class I into three types and placing the remainder of Arneth's classification in class IV; I, myelocyte; II, young form; III, band form; IV, all segmented varieties.

In 1920, von Schilling,[2] of Berlin, after a thorough application of Arneth's methods, published a modification of his classifications. He divided Arneth's class I into three types, the earliest form a
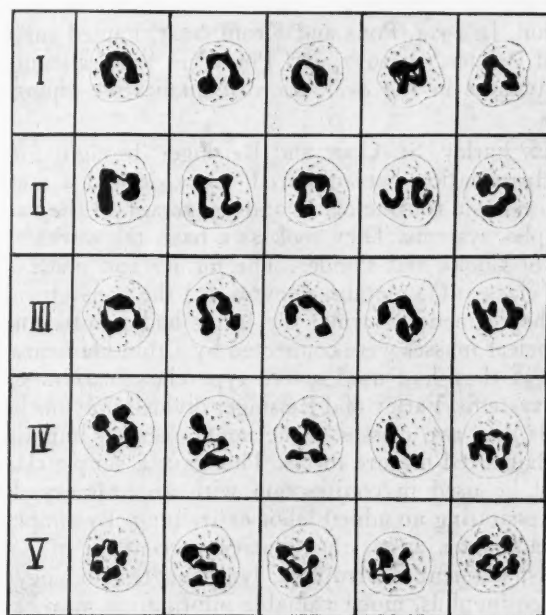

Fig. 3 — Classification of Cooke and Ponder, dividing polymorphonuclear neutrophils into five types, each type being designated by the number of divisions in the nucleus, noting that each nuclear segmentation was connected by a very fine filament of chromatin material. From Cooke and Ponder: The Polynuclear Count.

myelocyte, the second a young form and the third and more advanced a band form. His fourth type included all segmented varieties. A count of this type can be made in five minutes and is of great clinical value. It is surprising that von Schilling's modification has not come into more general use, for wherever it has been instituted its popularity has been immediate and its continued use assured. Von Schilling also noted typical toxic changes occurring both in the nuclear and in the granular elements of the young polymorphonuclears. The granules were larger and more deeply staining, and the nuclei tended to assume more bizarre forms. In addition, the cells were found to be more fragile and occasionally fat droplets and vacuole inclusions were found in the nuclei. These changes he did not consider of as great practical value, however, as the "nuclear shift," since they occurred before the crisis and remained after the crisis and were indicative of degenerative changes in the bone marrow.

Other workers presented various modifications of Arneth's classification. In 1924, Pons and Krumbhaar[3] named three classes; Cooke and Ponder,[4] in 1927, and Piney,[5] in 1928, also made noteworthy advances in the evaluation of qualitative changes in the leukocytes.

In 1930, Farley, St. Clair and Reisinger[6] brought forward the simplest classification yet advanced. They desired a method that could be used as a routine count and yet retain all the value of the more complex systems. They took as a basis the works of Krumbhaar and of Cooke and Ponder. The former had made a division into three classes: (1) metamyelocytes, (2) the nonsegmented types and (3) the segmented forms; the latter had pointed out that all divided nuclear masses were connected by a thin filament of nuclear material but they had used a five type classification. Combining these two systems, Farley and Reisinger divided polymorphonuclear neutrophils into two classes — the nonfilamented immature forms and the filamented mature forms. This gave a simple classification that could be used in conjunction with an ordinary differential count, necessitating no added labor or training. By simply classifying the leukocytes as to the relative percentage of nonfilament neutrophils, filament neutrophils, lymphocytes, monocytes, basophils and eosinophils, much valuable information may be added to the routine differential count.

Farley, St. Clair and Reisinger, in studying the blood of 100 normal adults by the method described, found that an approximate normal upper limit of nonfilament percentage could be set at 16. They also pointed out its value in diagnosing the presence of cryptic

infections and as added presumptive evidence in cases of malin-
gering.

The foregoing classification was used in the cases presented'in
this paper because of its simplicity of procedure while retaining all
the valuable information of the former more complex methods.
A slight modification was made in that instead of basing our ob-
servations on a count of 100 leukocytes, figures are reported on 100
polymorphonuclear neutrophils counted as well.

TABLE I
Maximum Nonfilament Percentages

Disease	Non-filament Percentage	Total Leukocyte Count
Hemolytic streptococcic septicemia	60	4,200*
Hemolytic streptococcic septicemia	72	32,000*
Acute appendicitis	21	15,000
Acute appendicitis	42	23,000
Acute appendicitis	20	11,600
Acute appendicitis	30	16,000
General peritonitis	64	3,000*
Hemolytic streptococcic sore throat	46	9,250
Lobar pneumonia	50	33,200*
Acute pansinusitis	42	9,800
Acute sinusitis (frontal)	22	10,600
Acute sinusitis (maxillary)	15	17,800
Acute sinusitis (frontal and maxillary)	17	9,400
Acute sinusitis (maxillary)	31	12,050
Acute sinusitis (maxillary)	27	11,600
Acute mastoiditis	72	36,200*
Acute mastoiditis	39	20,200
Acute mastoiditis	51	19,800
Acute mastoiditis	36	11,900
Acute mastoiditis	26	16,400
Acute mastoiditis	30	10,800
Acute mastoiditis	62	15,000*
Multiple furuncles	26	16,200
Septic hip	18	14,600
Ruptured gastric ulcer	68	12,200*
Acute cervical adenitis	18	14,300
Acute cervical adenitis	17	14,600
Erysipelas	53	21,000
Acute tonsillitis	35	15,200
Acute labyrinthitis	12	8,800
Acute mediastinitis (following laryngectomy)	54	19,200*
Intestinal obstruction	35	27,800*

*Death occurred.

It will be of interest, perhaps, to outline first the exact method
which we use for preparing a satisfactory smear for use in making

this count. Glass cover slips are prepared by thoroughly cleaning them with a rough cleaner such as Dutch Cleanser — this may be done in the palm of the hand, fifty or so slips being cleaned at a time. The cover slips are then rinsed in two washings of distilled water and placed in absolute alcohol for two or three minutes, after which they are dried and polished with a soft cotton cloth. Just before they are used, all dust particles are removed with a fine camel's hair brush. A small drop of blood is obtained in the usual manner and picked up with a cover slip placed in contact with the bleeding point. This cover slip is then dropped on a second cover slip, the drop of blood being allowed to spread out to cover almost
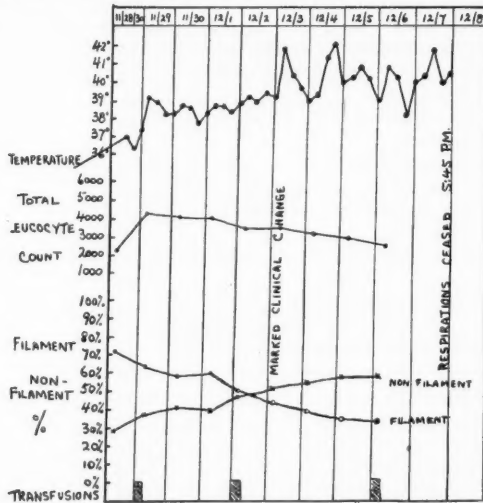

Fig. 4 (case 1) — Hemolytic streptococcic septicemia, generalized hemorrhages, with increasing nonfilament count over 50 per cent, terminating fatally.

the whole area of the slides, when they are gently pulled apart by a sliding motion, one over the other. A thin, even smear will be obtained on the opposing surfaces. Four or six of these smears should be secured on each occasion to be sure of obtaining a good smear. They are then stained by the Wright method, aided by a sodium and potassium phosphate solution with a pH of 6.6. The smears are then dried, mounted on a glass slide with gum damar and examined under oil immersion.

We have attempted in the cases here reported to attach a prognostic value to this count and our conclusions are based on the study of some thirty cases of acute infection taken from all

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services in the hospital. In all instances in which it was possible to do so, daily counts were made and also total leukocyte counts. It would take too much time to discuss each case in detail; consequently the cases studied, with the maximum nonfilament percentage found in each instance, are given in table 1, and a detailed discussion is given of ten of these cases, the majority of which are from services other than the otolaryngologic service, but chosen because they best illustrate the point in question. On examination of fifteen control smears from healthy adult individuals, a range of nonfilament percentages of from 8 to 16 was found, with an average of 12.1 per cent.

TABLE 2
Blood Examinations in Case 1

Date	Red Blood Cells	Total Leukocyte Count	Differential	NonFilament Percentage	Filament Percentage
11–28–30	2,740,000	2,600	82% P.; 16% L.; 2% E.	30	70
11–29–30	---------	4,200	72% P.; 23% L.; 4% E.; 1% B.	38	62
11–30–30	---------	4,000	72% P.; 26% L.; 2% E.	42	58
12– 1–30	---------	4,000	74% P.; 14% L.; 3% E.; 9% M.	41	59
12– 2–30	---------	3,800	76% P.; 20% L.; 1% E.; 3% M.	48	52
12– 3–30	---------	3,600	82% P.; 18% L.	53	47
12– 5–30	---------	3,000	79% P.; 17% L.; 1% B.; 3% M.	56	44
12– 6–30	---------	3,200	84% P.; 14% L.; 2% M.	60	40

Case 1.— A man, aged 35, admitted to the clinic, November 28, 1930, complained of shortness of breath, masses on the thighs and groins, hemorrhage from the nose, and severe furunculosis of the face. Physical examination showed the spleen to be markedly enlarged and extensive areas of hemorrhage were present in the
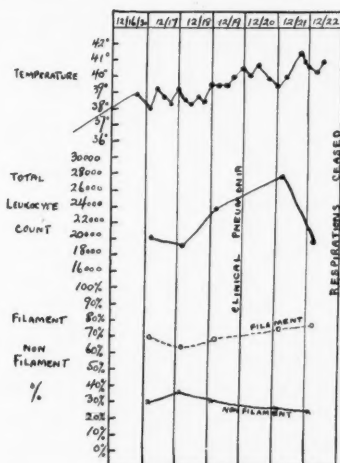

Fig. 5 (case 2) — Acute intestinal obstruction and general peritonitis with constant high nonfilament count.

subcutaneous tissues of the arms, trunk and legs; there were large areas of furunculosis on the face and marked hemorrhage from the mucous membrane of the nose and throat.

The patient was vomiting blood, but no blood was found in the stools or urine. The patient died, December 7th.

Here is pictured plainly a steadily increasing nonfilament count terminating in death, the nonfilament change preceding the changes in clinical symptoms, as seen in figure 4.

Pneumonia was noted clinically, December 3, with no change in the differential or white blood count, but a rise of 7 per cent in the nonfilament count preceded this condition by twenty-four hours.
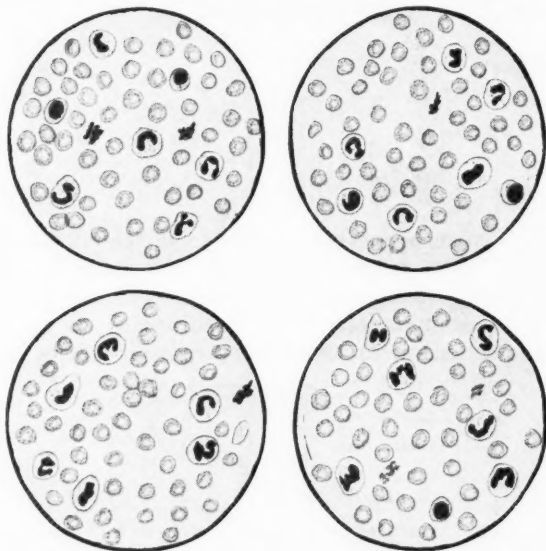
Fig. 6 (case 2) — Toxic changes in the nuclear structure of the polymorphonuclear neutrophils in a case of ruptured gastric ulcer and general peritonitis on the first, third, fourth and sixth days.

This case is a good example of the additional information that may be obtained from a count of this type. Postmortem examination revealed hemolytic streptococci from the heart's blood, although blood cultures during the course of the illness were repeatedly negative, terminal pneumonia and hemorrhages from all the mucous surfaces being the final cause of death.

Case 2.— A woman, aged 60, was admitted to the Cleveland Clinic Hospital with a history of severe pain in the right upper

quadrant, associated with nausea and vomiting, persisting for five days previous to admission. The vomitus had a fecal odor and no gas or feces had been passed by the rectum. An enema given two days previous to her admission had returned blood-stained but clear. For two days previous to the patient's admission there had been no vomiting. Marked distention was present. The patient was never in a condition for operation during her stay in the hospital.

In this case is found rather than a steady increase, a constant high nonfilament percentage, beginning at over 30 with a gradual terminal fall. This is not a typical example of the increasing nonfilament percentage, but an interesting point in this case was the presence of marked toxic changes in the nuclei as illustrated in figure 6.

TABLE 3
Blood Examinations in Case 2

Date	White Blood Cells	Differential	Non-Filament Percentage	Filament Percentage
12-17-30	20,000	84% P.; 13% L.; 3% M.	30	70
12-18-30	19,800	87% P.; 10% L.; 3% E.	35	65
12-19-30	24,000	86% P.; 8% L.; 4% E.; 2% M.	30	70
12-21-30	27,800	89% P.; 7% L.; 2% E.	28	72
12-22-30	20,200	94% P.; 4% L.; 2% M.	25	75

The patient showed steadily increasing weakness and toxicity, but, as has been pointed out, she was in no condition for operative intervention. Although a high white blood count was present throughout the disease, the marked change in the nonfilament percentage is not seen, perhaps because of the decrease in bone marrow activity. The patient died on the sixth hospital day.

Case 3.— A man, aged 62, was admitted to the clinic, November 7, 1930, with a history of having had glands removed from his neck eleven months previously, the condition having been diagnosed at that time as carcinoma. The immediate history included hoarseness for two months and marked difficulty in breathing for one week. Tracheotomy was performed on the day the patient was admitted and laryngectomy five days later. Infection occurred from the mouth through a pharyngeal fistula, and mediastinitis followed in spite of all treatment.

The patient was not seen until infection was well advanced, but the rapid rise seen on the second count was of grave prognostic significance even before the clinical picture was indicative of a possible fatal issue.

November 28, clinical bronchopneumonia was present late in the day, whereas a marked rise had already been noted in the nonfilament percentage that morning. The persistent high level of non-
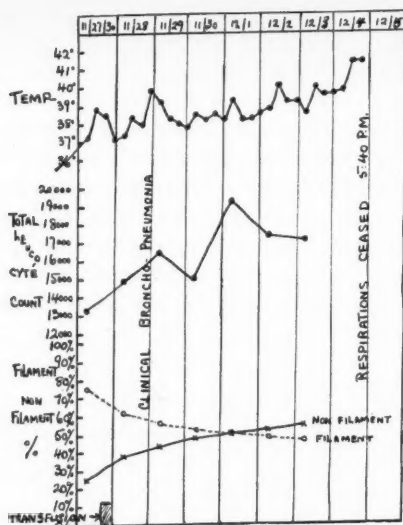
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Fig 7 (case 3) — Acute mediastinitis and bronchopneumonia following laryngectomy, showing increasing nonfilament count, terminating fatally.

TABLE 4
Blood Examinations in Case 3

Date	White Blood Cells	Differential	Non-Filament Percentage	Filament Percentage
11–27–30	13,200	84% P.; 13% L.; 2% E.; 1% B.	25	75
11–28–30	14,800	86% P.; 12% L.; 2% M.	38	62
11–29–30	16,400	85% P.; 21% L.; 1% B.; 2% E.	44	56
11–30–30	15,000	88% P; 10% L.; 1% E.; 1% M.	48	52
12– 1–30	19,200	95% P.; 5% L.	50	50
12– 2–30	17,450	85% P.; 13% L.; 2% M.	52	48
12– 3–30	17,200	84% P.; 13% L.; 3% M.	54	46

filament cells slowly increasing to 50 per cent is well illustrated here in a case which terminated fatally.

Case 4.— A man, aged 32, entered the clinic suffering from a typical attack of appendicitis of sixteen hours' duration. The course of examinations of the blood during his hospitalization is shown in table 5.

Here is seen the gradual steady return to normal percentage of the nonfilament cells in an uncomplicated case of acute appendicitis. As seen in figure 8, the white blood count showed a very rapid drop in twenty-four hours, January 5, 1931. Although clinical signs of bronchopneumonia were recorded on this date, the lungs were perfectly clear the following day and the temperature returned to
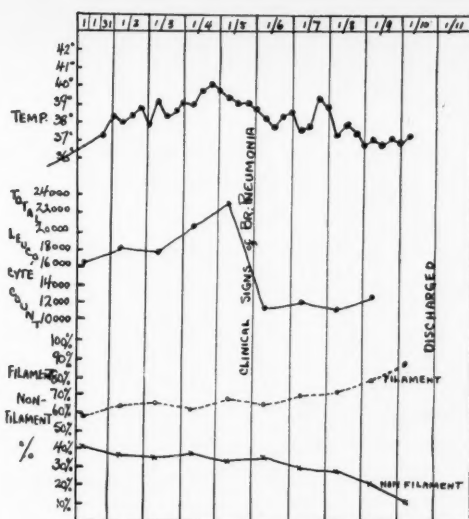
68

Fig. 8 (case 4) — Acute appendicitis, showing steady decrease of nonfilament count to normal in uncomplicated convalescence.

TABLE 5
Blood Examinations in Case 4

Date	White Blood Cells	Differential	Non-Filament Percentage	Filament Percentage
1- 1-31	16,800	---	42	58
1- 2-31	18,000	---	36	64
1- 3-31	17,800	---	35	65
1- 4-31	20,600	---	37	63
1- 5-31	23,000	93% P.; 6% L.; 1% M.	33	67
1- 6-31	10,800	82% P.; 15% L.; 1% E.; 2% M.	35	65
1- 7-31	11,000	80% P.; 18% L.; 2% M.	22	78
1- 8-31	11,200		28	72
1- 9-31	12,400	76% P.; 18% L.; 2% E.; 4% M.	21	79
1-10-31	10,200	78% P.; 18% L.; 4% M.	12	88

normal. The nonfilament count showed no change for the worse at this time, and it is hardly likely that any degree of infection was present in the lungs. The patient made satisfactory postoperative progress.

Case 5.— A man when first seen was complaining of severe cold in the head, of ten days' duration; headache was a marked symptom, accompanied by a profuse nasal discharge. Treatment was instituted and a large amount of pus was obtained by suction from both nostrils.

On the fourth day of observation the left maxillary antrum was irrigated without difficulty through the natural opening. The
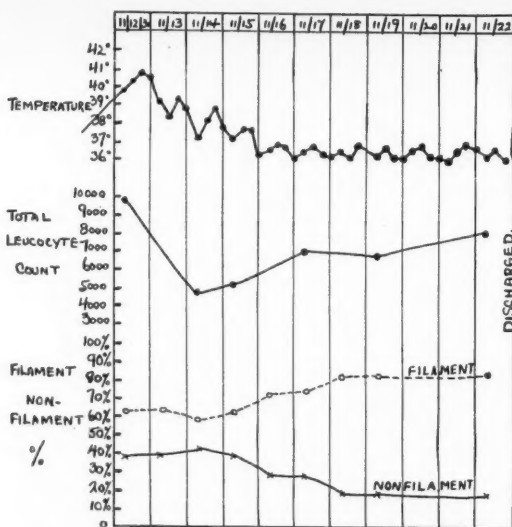
Fig. 9 (case 5) — Acute bilateral maxillary sinusitis, showing steady return of nonfilament count to normal during convalescence.

TABLE 6
Blood Examinations in Case 5

Date	White Blood Cells	Differential	Non-Filament Percentage	Filament Percentage
11–12–30	9,800	91% P.; 9% L.	38	62
11–13–30	------		38	62
11–14–30	4,805	72% P.; 28% L.; 1% B.	42	58
11–15–30	5,200	65% P.; 34% L.; 1% E.	38	62
11–16–30		70% P.; 24% L.; 4% E.; 2% B.	28	72
11–17–30	7,000	70% P.; 28% L.; 2% E.	27	73
11–18–30			18	82
11–19–30	6,800	82% P.; 15% L.; 3% E.	17	83
11–22–30	8,000	66% P.; 28% L.; 2% M.; 2% E.	16	84

return was clear. Reaction occurred the following day, the temperature rising to 102 F.; chills occurred.

Conservative treatment was followed and after a week, when marked evidence of sinus involvement was present, the left antrum was again irrigated and a large amount of pus obtained. The following day the patient again suffered a severe reaction and was admitted to the hospital.

The patient showed steady improvement after the third day, as evidenced by the temperature curve and the nonfilament percentage. This improvement, however, is not reflected in the total leukocyte count. This case is also an interesting example of the reactions that may follow the simple washing of an acutely infected sinus.

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Case 6.— A man was admitted to the hospital in a critical condition, suffering from severe abdominal pain and general collapse of three days' duration. Immediate operation was performed and a ruptured gastric ulcer with localized peritonitis was found. Repair and drainage were instituted and the patient made satisfactory progress until the third postoperative day.

TABLE 7
Blood Examinations in Case 6

Date	White Blood Cells	Differential	Non-Filament Percentage	Filament Percentage
12- 9-30	12,000	88% P.; 11% L.; 1% M.	68	32
12-10-30	11,000	85% P.; 14% L.; 1% B.	64	36
12-11-30	12,200	88% P.; 10% L.; 1% E.; 1% M.	30	70
12-12-30	7,800	83% P.; 14% L.; 3% M.	43	57
12-13-30	6,400	85% P.; 12% L.; 3% M.	48	52
12-14-30	8,700	87% P.; 7% L.; 2% E.; 4% M.	39	61
12-15-30	8,600	78% P.; 21% L.; 1% M.	42	58

Here is seen an acute abdominal condition with a very high nonfilament percentage before operation. Following operation and drainage, the nonfilament percentage gradually fell until the third postoperative day, when a marked rise was noted. Later on this day the patient's general clinical condition was markedly worse. Complications were suspected and on examination of the wound and abdomen a breaking down of the operative area was found and a diagnosis of general peritonitis was made. In spite of all treatment, the patient became steadily worse, the nonfilament count rising again with a fatal termination.

The total leukocyte count here again was never as high as one would suspect from the clinical picture, ranging, as seen in figure 10, from 6,000 to 12,000 and not following the clinical course as did the filament-nonfilament count.

Case 7.— A man, giving a typical history of acute appendicitis, was operated on immediately after his admission to the hospital.

Table 8 shows the white blood count fluctuating quite markedly throughout the convalescence, but the patient showed very satisfactory postoperative progress, with the rapid return of the nonfilament relation to normal.

TABLE 8
Blood Examinations in Case 7

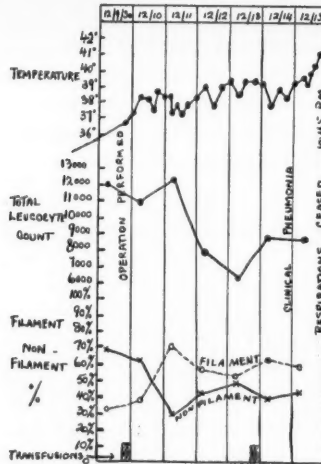| Date	White Blood Cells	Differential	Non-Filament Percentage	Filament Percentage
12- 8-30	15,000	86% P.; 12% L.; 2% M.	31	69
12- 9-30	11,000	85% P.; 15% L.	19	81
12-10-30	12,400		15	85
12-11-30	8,200		18	82
12-12-30	12,600		14	86
12-13-30	11,000		12	88
12-14-30	10,200			
12-16-30	9,500		12	88

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Fig. 10 (case 6) — Ruptured gastric ulcer and general peritonitis illustrating fatal termination with high nonfilament count and secondary rise of nonfilament count indicating complications.
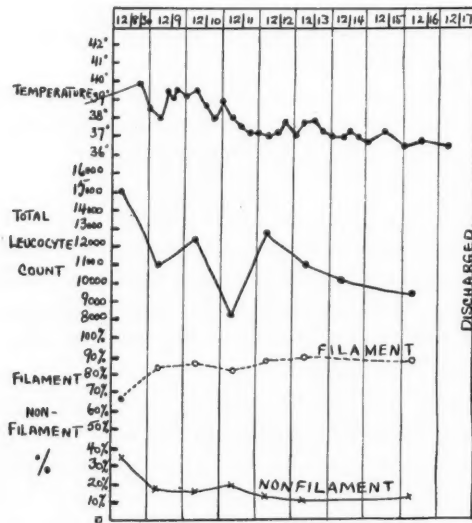

Fig. 11 (case 7) — Acute appendicitis, showing return of nonfilament count to normal in uncomplicated convalescence.
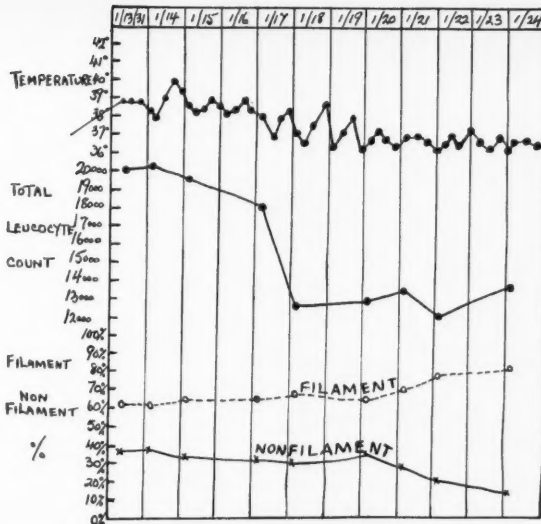
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Fig. 12 (case 8) — Acute mastoiditis, showing steady return of nonfilament count to normal in uncomplicated convalescence. The patient was discharged, January 25, 1931.

TABLE 9
Blood Examinations in Case 8

Date	White Blood Cells	Differential	Non-Filament Per-centage	Fila-ment Per-centage
1-31-31	20,000	80% P.; 18% L.; 2% M.	38	62
1-14-31	20,200		39	61
1-15-31	19,500		35	65
1-17-31	18,000	88% P.; 12% L.	32	68
1-18-31	12,400	77% P.; 16% L.; 3% E.; 4% M.	31	69
1-20-31	13,000	79% P.; 16% L.; 1% E.; 4% M.	33	67
1-21-31	13,800		30	70
1-22-31	12,200		24	76
1-24-31	14,000		16	84

Case 8.— A boy, aged 12 years, was admitted to the clinic with a typical history of acute mastoiditis. Operation was performed and the patient's convalescence was very satisfactory.

This case is an example of satisfactory convalescence following operation in acute mastoiditis. Here again the nonfilament count follows closely the clinical improvement.

Case 9.— A woman, aged 35, was admitted to the clinic with an acute abdominal condition. The history was generally unsatisfactory. A diagnosis of general peritonitis was made, but the clinical picture was not critical, although the patient's temperature on admission was 104 F. The blood examinations in case 9 is shown in table 10.
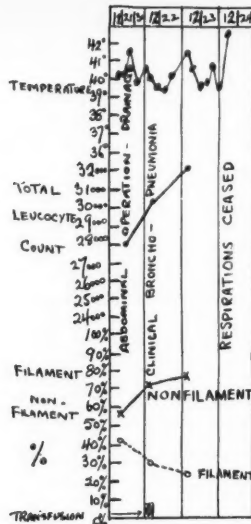
Fig. 13 (case 9) — General peritonitis, illustrating high nonfilament count in fatal case.

TABLE 10

Blood Examinations in Case 9

Date	White Blood Cells	Differential	Non-Filament Per-centage	Fila-ment Per-centage
12–21–30	28,000	99% P.; 1% L.	58	42
12–22–30	30,200	93% P.; 5% L.; 2% M.	70	30
12–23–30	32,000		72	28
12–24–30	Death			

Table 10 shows a very high nonfilament percentage on admission but a clinical picture that is not critical. The patient seemed to be in good condition generally, was not extremely toxic, and the heart and lungs were normal. On the second day, the patient's clinical condition was much worse, with early signs of bronchopneumonia and general collapse. She became rapidly worse and died on the fourth hospital day. This case illustrates the high nonfilament count giving a poor prognosis twenty-four hours before the clinical conditions became alarming.

Case 10.— A boy, aged 6 years, gave a history of acute pain in the right ear six weeks previous to admission. The right ear had been discharging during this period and periodic attacks of chills and high temperature occurred. The diagnosis was acute mastoiditis with probable sinus thrombosis and blood stream infection, although the patient's condition appeared to be good.
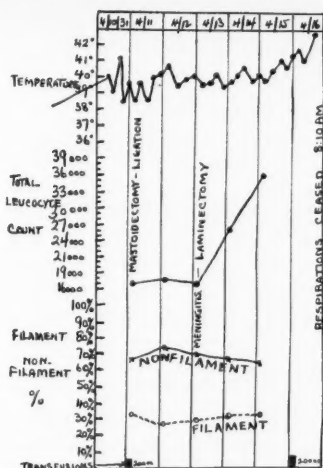
74

Fig. 14 (case 10) — Acute mastoiditis with jugular thrombosis and meningitis, showing constant high nonfilament count with a fatal termination.

TABLE 11
Blood Examinations in Case 10

Date	White Blood Cells	Differential	Non-Filament Percentage	Filament Percentage
4–11–31	17,000	78% P.; 22% L.	66	34
4–12–31	17,200	81% P.; 15% L.; 4% M.	72	28
4–13–31	17,000	82% P.; 14% L.; 4% M.	70	30
4–14–31	26,600	92% P.; 6% L.; 2% M.	68	32
4–15–31	36,200	88% P.; 6% L.; 6% M.	66	34

TABLE 12
Nonfilament Counts in Infectious and Noninfectious Types of Arthritis

Case	Noninfectious, Per Cent	Infectious, Per Cent
1	----	14
2	----	15
3	8	----
4	----	13
5	9	----
6	----	22
7	----	29
	17	93
Average	8.5	18.6

TABLE 13
Eosinophilic Percentage in Allergic Phenomena

Case	Protein Sensitization, Per Cent	Infectious, Per Cent	Eosinophils, Per Cent
1	----	16	3
2	----	25	12
3	7	----	6
4	15	----	4
5	----	18	7
	22	59	
Average	11	19.6	

75

On operation, the patient was found to have a very acute mastoid condition, with thrombosis of the lateral sinus extending down the jugular vein almost to the level of the clavicle. A mastoid operation was performed, the lateral sinus exposed and the jugular vein tied off. Postoperatively, an abscess developed about the jugular vein with meningitis, and the child died on the sixth postoperative day.

This is another example of an extremely high nonfilament count with a total leukocyte count lower than would be expected. Here, again, is found a very high nonfilament count at the beginning of the period of observation, which, following operation, dropped in only a slight degree; although the nonfilament percentage showed a slow decrease, it was so high at the onset that a favorable prognosis could not be expected.

Seven cases of arthritis were studied to see whether any change could be noted in those cases in which the condition could be definitely attributed to an infectious origin. The results were rather promising in that those cases of the infectious type showed an average nonfilament count of 18.6 per cent, whereas the cases of noninfectious origin showed an average count of only 8.5 per cent. The individual counts are shown in table 12.

Table 12 brings out the possibility of an aid to differentiation in this type of case in which any added information is of definite value.

A limited number of cases of allergic phenomena were also studied, and it was found as a general rule in cases in which the asthma could be attributed to foci of infection that the nonfilament count was higher than in those cases in which the condition could be traced to definite protein sensitization.

In these cases, also, the eosinophilic percentage was interesting in that practically all showed eosinophils of over 4 per cent.

We were greatly interested in the observations of Dr. G. A. Winfield,[7] of the Cleveland Clinic, in his work on malarial treatment of syphilis. In these cases, nonfilament counts were observed following inoculation with the malarial parasite and very high percentages were noted, ranging as high as from 70 to 80 per cent of nonfilament forms with a marked leukopenia. This was extremely interesting in that none of these cases terminated fatally. It was interesting to note the rapidity with which the changes occurred and also the constancy with which the nonfilament percentage followed the course of the reactions. Dr. Winfield notes the nonfilament percentage to be the most constant blood picture in this treatment.

Conclusions

1. The filament-nonfilament count as outlined is a valuable aid in securing the clinical picture of disease, following more closely the course of the infection than the total leukocyte count and foretelling complications in convalescence.

2. In nonfilament counts of 50 per cent and over, a very guarded prognosis must be given. The majority of such cases reach a fatal termination.

3. Filament-nonfilament counts may prove valuable aids in the differential diagnosis of infections from non-infectious allergies and arthritides.

4. Filament-nonfilament counts may prove a valuable basis by which to gage the dosage of malarial injection in the treatment of syphilis.

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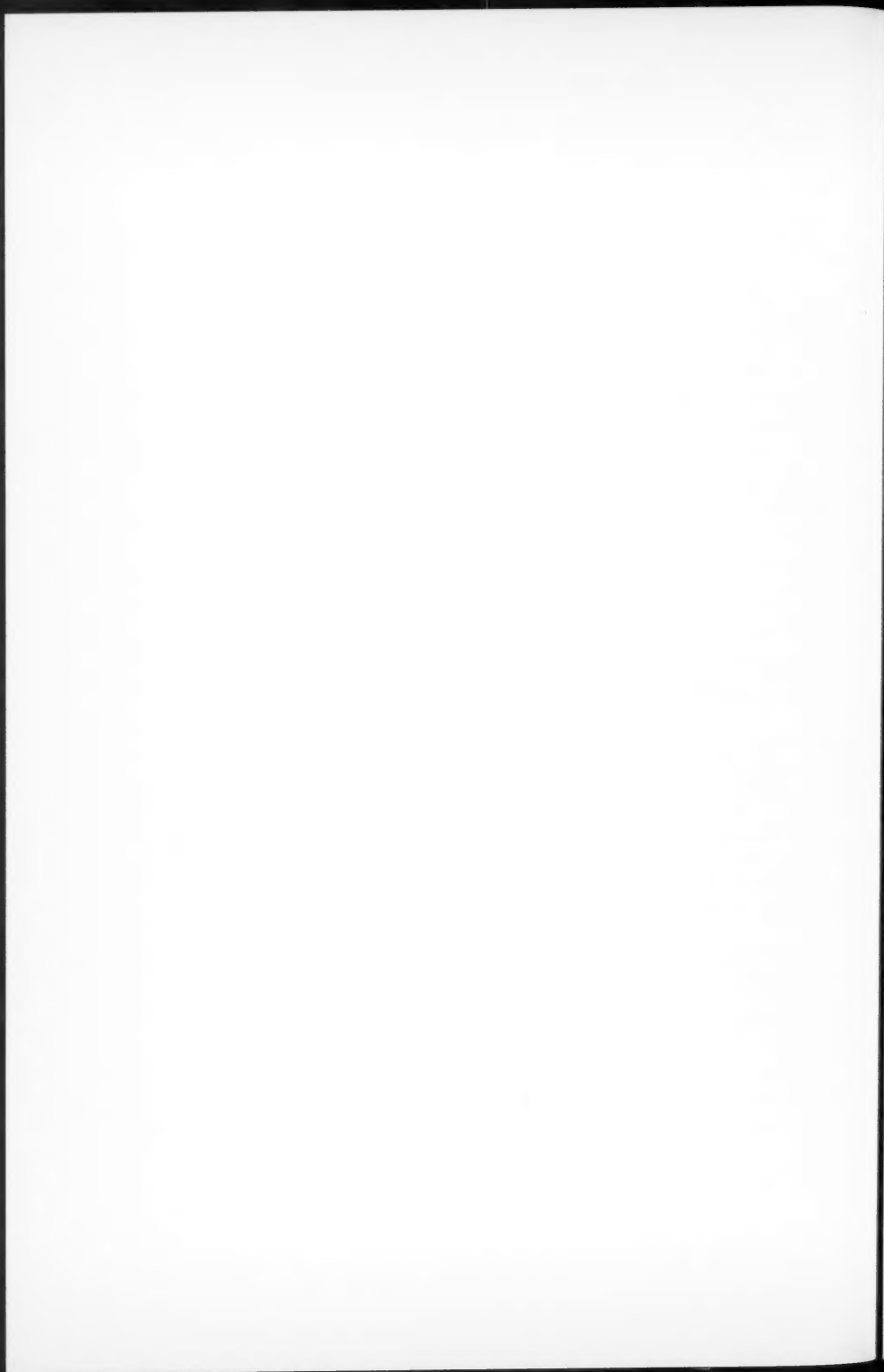
THE COMPARATIVE VALUES OF RETROGRADE AND INTRAVENOUS UROGRAPHY

Bernard H. Nichols

The historical background for the visualization of the urinary tract by means of the injection of an opaque medium is well known from the time of von Lichtenberg's[1] pyelography to the present era of intravenous urography. However, one incident of experimentation in the evolution of this diagnostic procedure should be borne in mind in every discussion of the subject, and that is the work of Osborne, Sutherland, Scholl, and Rowntree,[2] who in 1923 performed intravenous pyelography using sodium iodide. Owing to the imperfections of their preparations, however, they were unable to make the procedure practical.

The preparations which are in use at the present time are stable, organic iodide compounds. The first of these was selectan neutral which was introduced by Binz and Rath[3] in 1925 for the purpose of combating coccus infections. By the intravenous use of this agent they were able to visualize the urinary tract and this led to further efforts to obtain a product of less toxicity which would be capable of greater concentration. Roseno[4] came forward with pyelognos, which however, was not satisfactory, and it was left for Swick,[5] of New York, to perfect a preparation which he called uroselectan. This preparation proved to be of practical application and immediately intravenous pyelography became a prominent roentgenologic procedure. Since then the preparations of skiodan and abrodil have been brought into use. These contain 52 per cent of iodine as compared with uroselectan which contains only 40 per cent. The latest preparation, neo-iopax, is in solution and may be injected directly from the sealed ampoule.

It is possible by means of these newer preparations to use an injection of 20 gr. as against the 40 gr. necessary with the former preparation. The total quantity of solution used in each instance, however, is 100 c.c. which is injected by the gravity method. In our experience no untoward reaction has followed this procedure.

These later preparations are excreted more rapidly which necessitates taking films immediately after the injection and at more frequent intervals than was necessary with the old preparations.

Urography by the intravenous method is a practical procedure with almost no contraindications except in cases of glomerular

nephritis where excretion is at the minimum. By this method the entire urinary tract may be visualized. A very accurate determination may be made of the integrity of the kidney and its ability to excrete through the glomeruli, amounting to virtually a visual estimation of kidney function.

While this method does not give a precise result, von Lichtenberg states that it is satisfactory for clinical interpretation and judgment of a surgical lesion. Perhaps a fair estimate of elimination is about 90 per cent in the first hour, and in cases in which no concentration is shown in the first half hour, the kidneys may be definitely considered to be functionally impaired.

Intravenous urography then becomes a wonderful complement to cystoscopy and should be considered as an adjunct to the older methods of examination. On the other hand, its indiscriminate use as a short cut to diagnosis must be condemned, and it should in no sense be considered as comparable with pyelography by the catheter method; but its use is definitely indicated where retrograde pyelography can not be done, or where both kidneys are to be investigated and bilateral injection is contra-indicated.

The visualization of the kidney pelvis and ureters by intravenous urography is of necessity only a functional process and may be compared to the colon examination made after an ingested opaque medium which usually shows the colon partly filled in contrast to that in which the colon is completely filled with a barium enema. This at once gives us some idea of the comparative difficulties in interpretation, particularly in the case of the normal kidney, when perhaps only 50 per cent are filled sufficiently to rule out disease.

It would seem then that catheterization and injection of the kidney pelvis and ureters is the method of choice in the vast majority of pyelographic examinations, as by this method specimens may be obtained from both sides, which is particularly advantageous in cases of infection.

There are many cases, however, in which catheterization is impossible or at least impractical. These might be divided broadly into three classes: (1) cases in which anatomical or pathological conditions preclude cystoscopy, (2) when obstruction prevents injection of the solution beyond the point of obstruction, and (3) those cases in which instrumentation becomes a risk to the patient. To enumerate some of these conditions more explicitly we would first mention cases in which the ureters have been transplanted into the colon; cases of ureteral obstruction, such as a large stone; stricture of the ureter; or tumor of the ureter (in many of these cases it is

extremely important to know something of the condition of the kidney and ureter above the point of obstruction); diverticulosis of the bladder in which the ureter opens into the diverticulum and the introduction of a ureteral catheter is impossible; extensive papillomata or other tumors of the bladder, which obscure the ureteral orifice; enlarged prostate or stricture of the urethra, making cystoscopy impossible; the presence of only one kidney, either a congenital solitary kidney or a single kidney left after nephrectomy (in these cases the urologist many times hesitates to do a pyelogram on the only remaining kidney); cases of marked cystitis with edema of the bladder wall, sometimes with marked hematuria; tuberculosis of the kidney in the presence of which many authors consider it inadvisable to do bilateral pyelography.

Many times the suspected kidney may be examined by retrograde pyelography and the pathology definitely determined, yet it becomes of importance to determine the kidney function and the possibility of a similar infection in the opposite kidney. In many instances this can be very nicely done by intravenous urography. Anomalies of the kidneys and ureters may be very well demonstrated by this method, particularly polycystic kidneys which are usually bilateral and have a rather poor function; also in the case of nervous individuals where cystoscopy can not be performed without anesthesia. In the urologic conditions of childhood, intravenous urography should at least be the first procedure to be attempted and in most instances will give very definite information as to the condition of the urinary tract.

Many authors have cited hydronephrosis as an ideal condition for the demonstration of intravenous iodide. I wish to call your attention to the fact that most hydronephroses are of an intermittent type and unless such an examination is done at the time of actual obstruction there will be little or no retention and the amount of hydronephrosis present either will be missed entirely or be vastly underestimated.

Interpretations of urograms made by intravenous urography embody most of the principles of diagnosis or interpretation which are obtained by retrograde pyelography. There is this difference, however, that by the former method only the urine contained iodide is seen in the functional process and peristalsis may empty a single calyx or the ureter and thereby cause filling defects which may be interpreted incorrectly. To avoid this, a considerable number of films should be made as is done in a study of the duodenum after barium in an attempt to get a well filled duodenal bulb.

As previously stated, great care should be exercised in estimat-

ing the amount of hydronephrosis present in a given case or in deciding the presence of a moderate hydronephrosis which is often seen in ptosis of the kidney or any early obstruction of intermittent character as the kidney may be functioning well at the time of such an examination. The same applies to the extensive infection of the kidney with poor function. Calculi may be accentuated and more easily visualized by this method as compared with their complete obliteration in retrograde pyelograms. The anomalies are well determined and offer no great difficulty of interpretation.

SUMMARY

I feel that with some experience the findings from intravenous pyelograms, ureterograms and cystograms will offer only moderate difficulty. One may be discouraged by many unsatisfactory examinations but by perseverance these difficulties will be overcome, as has been the case in cholecystography due to improvement in technic and careful attention to details.

Intravenous urography, then, has added a very valuable method to our urological diagnostic armamentarium and has come to be a practical roentgenologic method of examination in cases in which a pathological condition in the urinary tract is suspected.

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SOLITARY CYSTS OF THE KIDNEY

Charles Clair Higgins, M.D.

Because of the apparent rarity of solitary cysts of the kidney it seems worthwhile to report ten cases from the records of the Cleveland Clinic. I use the term "apparent rarity" because it would appear that solitary cysts of the kidney are of more frequent occurrence than we are led to believe from a review of the literature. As Branch[1] states, solitary cysts of the kidney are rarely observed by the clinician but are frequently observed by the pathologist.
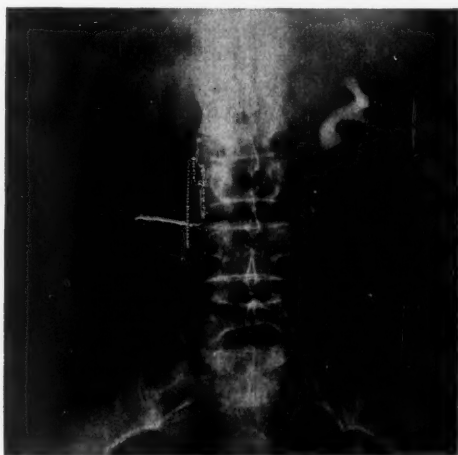

Fig. 1 — Pyelogram showing deformity of calices of kidney due to solitary cyst.

He states further that unless the cysts reach a sufficient size to produce pressure symptoms, they are rarely diagnosed and are found only at autopsy. Branch states that they are present in from 3 to 5 per cent of all autopsies. In five kidneys from thirty-six cadavers, Kampmeier[2] found cysts which varied from 2.5 to 5 centimetres in diameter. From 2,610 autopsies at the Middlesex Hospital, in London, Morris[3] reported five cases of solitary cysts. We have found in the literature reports of 158 cases. The addition of our ten cases brings the total number to 168.

Case I.— The patient was a woman forty years of age who entered the clinic complaining that during the preceding ten years she had suffered from pain in the right side and difficulty in urina-

tion, the latter symptom having followed childbirth. The patient also had a feeling of fulness in the abdomen and an occasional aching pain in the right side. For the preceding few years there had been marked urgency and nocturia. There was no history of hæmaturia.

The physical findings were normal except for a palpable smooth mass in the region of the right kidney. The roentgenogram showed a large round shadow connected to the lower pole of the right kidney.

The first pyelogram was normal, but a later one showed a spherical enlargement below the lower pole of the kidney (fig. I). Blood-pressure was 120/75, red blood count 4,400,000, white blood count 8,750, hæmoglobin 80 per cent, urine normal, Wassermann negative. The pre-operative diagnosis was cyst of the right kidney. At operation a cyst was found at the lower pole of the right kidney. This was removed together with a wedge of renal parenchyma. Convalescence was uneventful.

Case II.— A man, sixty-two years of age, entered the clinic complaining of jaundice which had been increasing in intensity during the preceding few weeks, but was not associated with pain. There was marked pruritus and the stools were clay-colored. For years he had been aware of a mass in the right side of the abdomen which had been diagnosed "ptosed liver." It had not caused pain but only a feeling of fulness.

Physical examination revealed a man in very poor physical condition who was quite jaundiced and acutely ill. In the right kidney region was a large round mass the size of a grapefruit, which was not nodular and was soft in consistency. Pyelography was not thought advisable. The blood-pressure was 140/90. Laboratory findings were as follows: hæmoglobin 80 per cent, red blood count 4,030,000, white blood count 6,950; blood urea 84; blood cholesterol 182; serum bilirubin 3.8 direct; urine — albumin two plus, 2 to 5 pus cells per high-power field, few granular casts; Wassermann negative.

A diagnosis of carcinoma of the head of the pancreas was made and an exploratory operation performed. In addition to carcinoma of the pancreas a large solitary cyst the size of a grapefruit was found at the lower pole of the right kidney. This was aspirated. The patient died a few days later of uræmia.

Case III.— A man, aged seventy-four, entered the clinic complaining of nocturia, frequency, difficulty in voiding, and blood in the urine. Recently he had noted terminal hæmaturia. He was poorly nourished; blood-pressure was 130/80. The only important finding on general and cystoscopic examination was marked enlarge-

ment of the prostate. *Laboratory findings* — Hæmoglobin 85 per cent, red blood count 4,350,000, white blood count 5,800; phenol-sulphonphthalein 40 per cent in two hours; blood urea 57; urine — albumin two plus, red blood cells 20 to 30, and white blood cells 2 to 5 per high-power field; Wassermann negative.

A suprapubic prostatectomy was performed, and the patient died four days later of pneumonia. Post-mortem examination revealed a cyst of the power pole of the right kidney which was filled with light amber-colored serous fluid. Pneumonia was the primary cause of death.

Case IV.— A man, seventy-nine years of age, entered the clinic complaining of difficulty in voiding. Five years ago he had first experienced increasing nocturia and difficulty in starting the stream which had diminished in size; terminal dribbling was quite pronounced. A poorly nourished man showing evidence of considerable loss in weight. Blood-pressure was 120/80. Heart moderately enlarged and a loud systolic blow was heard at the apex. Rectal examination revealed considerable enlargement of the prostate and cystoscopic examination showed marked intravesical projection of the prostate.

A perineal prostatectomy was performed. The patient died five days later of uræmia and pneumonia.

At post-mortem examination a large solitary cyst 18 centimetres in diameter and filled with serous fluid was found on the anterior surface of the upper pole of the right kidney.

Case V.— A man, twenty-four years of age, entered the clinic complaining of pain in the left kidney region which had continued intermittently for the preceding year. These attacks came on suddenly, lasting from ten to fifteen minutes and then subsiding. There was no hæmaturia or passing of gravel. Nothing of significance was found in the physical examination; no tumor mass was palpable. The cystoscopic examination led to the diagnosis of calculous pyonephrosis. *Laboratory findings* — Wassermann negative; blood normal; function test not recorded; urine — numerous pus cells, no red blood cells. A left nephrectomy was performed and in addition to the calculous pyonephrosis a cyst the size of a lemon was found at the lower pole of the kidney. Convalescence was uneventful.

Case VI.— A man, forty-six years of age, entered the clinic complaining of severe attacks of pain over the right kidney from which he had suffered for several years. The pain radiated downward toward the scrotum. There was no history of hæmaturia or passing of gravel. Physical findings were normal except for tenderness on deep pressure over the right kidney. *Laboratory findings* — Wasser-

mann negative, phenolsulphonphthalein 50 per cent in two hours. Urine — trace of albumin, white blood cells 2-4 per high-power field. A cystoscopic examination was done and a diagnosis of calculous pyonephrosis was made from the pyelogram.

A right nephrectomy was performed at which time a large solitary cyst containing clear, serous fluid, was found at the lower pole of the kidney in addition to the calculous pyonephrosis. This cyst was ruptured accidentally while removing the kidney.

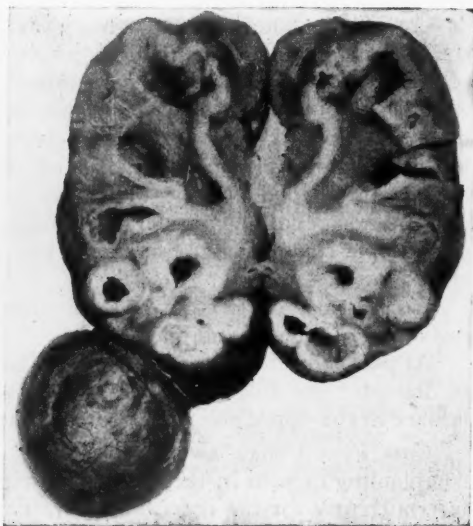Fig. 2 — Photograph showing a large cyst of the right kidney associated with tuberculosis.

Fig. 3 — Photograph of cut specimen of kidney with cyst attached.

Case VII.— A woman, forty-five years of age, entered the clinic complaining that for six months she had experienced urinary urgency, frequency every fifteen minutes and nocturia ten to twelve times. One month before entering the clinic she had passed a small amount of blood. There was no history of loss in weight. Two weeks previously she had had an attack of pain in the right side accompanied by chills and fever. She was a fairly well-nourished woman showing no evidence of weight loss. The blood-pressure was 130/90. Suprapubic tenderness was present. Vaginal examination revealed a hard, pencil-like, tender lower right ureter. A cysto-

scopic examination was made and tubercle bacilli were found in the specimen from the right kidney. From the pyelogram a preoperative diagnosis of tuberculosis of the right kidney was made. *Laboratory findings were as follows* — Wassermann negative; hæmoglobin 70 per cent, red blood count 4,420,000, white blood count 7,800; urine — pus two plus, red blood cells 5-10 per high-power field, phenolsulphonphthalein 18 per cent in fifteen minutes.

Nephrectomy was performed. The kidney was found to be tuberculous and a solitary cyst larger than an egg and containing yellowish, clear, serous fluid was found in the lower pole. Convalescence was uneventful. (figs. 2 and 3.)
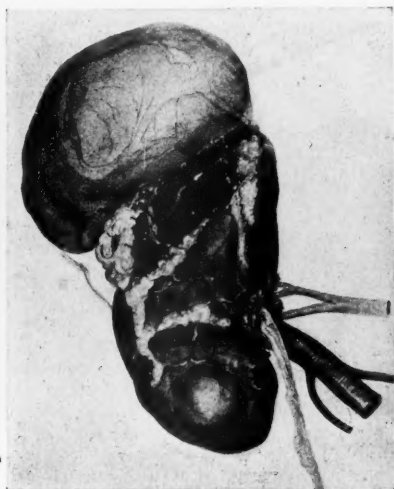

Fig. 4 (left) — Photograph of cyst attached to upper pole of left kidney found post-mortem in a patient who died of lymphatic leukaemia.
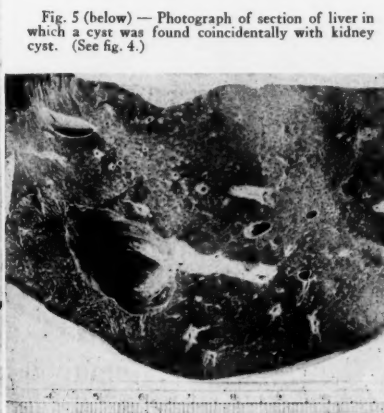
Fig. 5 (below) — Photograph of section of liver in which a cyst was found coincidentally with kidney cyst. (See fig. 4.)

Case VIII.— A man, sixty-four years of age, entered the clinic complaining of weakness and loss of weight. His general condition had been very poor for the preceding month and he had lost 20 pounds in weight.

He was very poorly nourished with a generalized glandular adenopathy. Blood-pressure was 124/80. The liver and spleen were both palpable.

Laboratory findings were as follows.— Hæmoglobin 70 per cent, red blood count 3,900,000, white blood count 70,000, smear of blood showed 71 per cent large lymphocytes; urine — albumin one plus, white blood cells two plus; Wassermann negative. A diagnosis of lymphatic leukæmia was made and x-ray therapy was instituted.

The patient died two months later. At post-mortem a large solitary cyst filled with clear, serous fluid was found at the upper pole of the left kidney (fig. 4).

It is interesting to note that a single cyst 3 centimetres in diameter containing clear, serous fluid was also found in the left lobe of the liver (fig. 5). No other cysts were found.

Fig. 6 (left) — Photograph of serous cyst of left kidney.

Fig. 7 (below) — Photograph of this cyst after it was removed.

Case IX.— A man, fifty-three years of age, entered the clinic complaining of stomach trouble, the symptoms of which had been present during the preceding two years. During this time he had had more or less constant pain in the left lower quadrant which he described as pulling-down pain. About one year ago he had had an attack of cramp-like pains in the left lower quadrant causing him to double up in agony, and six months previously he had had an acute attack of pain in the lower abdomen accompanied by vomiting.

He was well-nourished. Blood-pressure was 134/80. On physical examination the only finding of significance was a mass to the left of the umbilicus. This mass was round, movable, and not tender. A pyelogram showed a large mass connected with the lower pole of the left kidney. *Laboratory findings* — Red blood count 4,780,000, white blood count 7,800, hæmoglobin 85 per cent; urine normal except for a few pus cells; blood urea 48; phenolsulphonphthalein test showed normal excretion.

A pre-operative diagnosis of solitary cyst of the lower pole of the left kidney was made. At operation a cyst the size of a small grape-fruit was found attached to the lower pole of the left kidney (figs. 6 and 7). This was excised without removing any of the kidney parenchyma. Convalescence was uneventful.

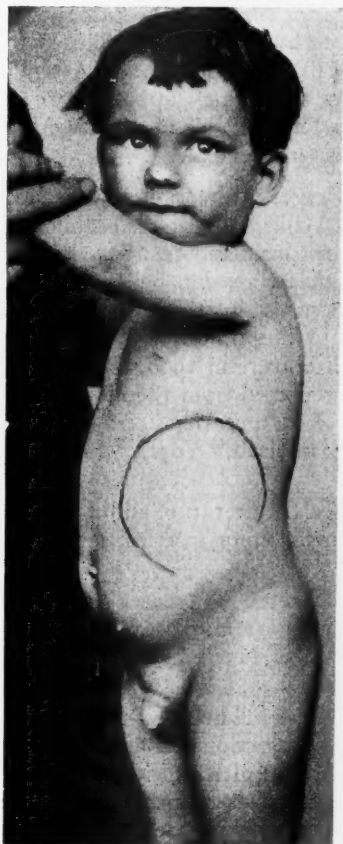Fig. 8 — Photograph of a boy three years old in whose case a diagnosis of malignant tumor of the kidney was made. Operation disclosed a cyst 13 by 10 by 9 centimetres.
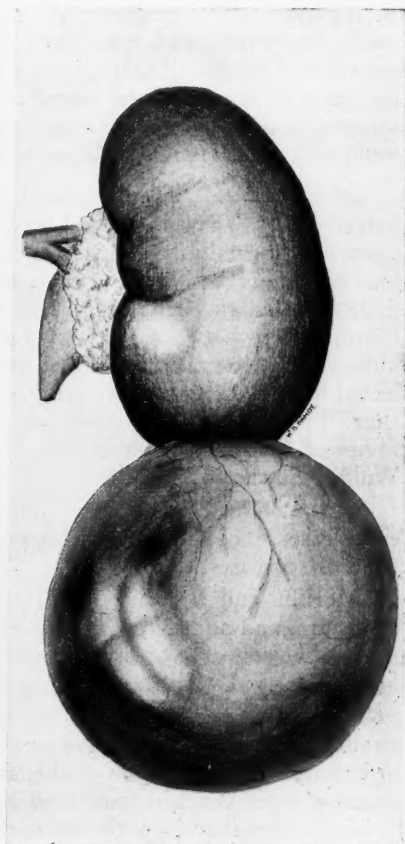
Fig. 9 — Drawing showing a solitary cyst at lower pole of kidney.

Case X.— A boy, three years of age, was brought to the clinic because of an enlargement of the abdomen. He had always been healthy but the abdomen has been protuberant since birth (fig 8).

On physical examination the only significant finding was a large mass the size of a grapefruit in the left hypochondrium. Upon roentgenographic examination this was shown to be a large mass in the region of the left kidney. Kidney function was normal as were the urinary findings. A pyelographic examination was not made.

A pre-operative diagnosis of malignant tumor of the kidney was made. At operation a large cyst 13 by 10 by 9 centimetres filled with serous fluid was found at the lower pole of the left kidney and extending upward on its lateral surface. As the kidney appeared to be atrophic it was removed with the cyst. The kidney and cyst together weighed 570 grams. Convalescence was uneventful.

Review of the Literature.— Solitary cysts of the kidney were first described by Fabry[4] in 1624. Thomas Willis,[5] the English clinician, described them in the seventeenth century, and in 1837 Rayer[6] first classified the various types, this classification being followed in 1876 by an excellent treatise by Lavaran[7] in which he discussed the difference between solitary cysts of the kidney and polycystic kidney. In a complete review of the literature in 1906, Simon[8] collected fifty-two cases which had been reported from 1860 up to that time. Later, individual cases were cited and the literature was reviewed by Caulk,[9] Cunningham,[10] Blanchard,[11] Vogel,[12] Beneke,[13] Wulff,[14] Fowler,[15] and others.

In 1920 Kretschmer[16] again reviewed the literature adding forty-eight cases, including one of his own, to Simon's series, making a total of 100 cases.

McKim and Smith,[17] in 1924, collected 117 cases from the literature, and added three. In the same year Harpster[18] presented ninety-five collected cases, in eighty-two of which an operation had been performed with the following results:

In thirty cases nephrectomy was done followed by recovery in twenty-three cases; in thirty-four cases, resection of the cyst alone, or together with a portion of the kidney, resulted in death in three cases or 9 per cent; in four cases the cyst was tapped followed by death in two cases. In the remaining fourteen cases the type of operation was not stated.

In 1928, Carson[19] collected 126 cases from the literature and added fifteen cases which had been reported between the years 1923 and 1927. These, with four additional cases made a total of 145.

In 1930, Grove[20] collected 153 cases from the literature, and added a case, and Kretschmer[21] recently reported five cases of his own. As we have stated the addition of the ten cases cited in this paper brings the total number up to 168.

Structure.— The wall of a solitary cyst of the kidney is generally grayish-white in color varying from one to five millimetres in thickness. Calcification is rare but may occur as in the case cited by Kirwin.[22] The inner surface is smooth and glistening and fine blood-vessels may be seen coursing through it (fig. 9). The wall of the cyst is independent of the capsule of the kidney, although frequently it is closely adherent to it. Some investigators state that the cyst has no epithelial lining while others describe the presence of a single layer of low, cuboidal epithelium. It has even been stated that the lining consists of normal cell formation of uriniferous tubules which, as the result of pressure, may be flattened.

In our series of cases the cell lining of the cysts varied. In one case the lining consisted of flattened cells separated by rather heavy connective-tissue trabeculæ. In another, the cyst wall was composed of fairly dense, fairly well vascularized, simple, fibrous, connective tissue but no epithelial cells were present. If the cyst is large, pressure atrophy may be present in the adjacent kidney tissue.

A cyst usually contains clear, straw-colored, serous fluid, the specific gravity of which is low. Hæmorrhage may take place into the cyst, producing blood clots. In one of our cases the fluid had a distinct odor of urine. Fowler states that the fluid contained in a cyst is clear, watery and albuminous, and does not contain urinary elements unless it communicates with the pelvis or calyces of the kidney, which is not the case as a general rule.

Age Incidence.— Carson states that the majority of cases of solitary cysts of the kidney occur between the ages of thirty and sixty years, the average age being forty-five. Simon also states that the condition occurs most frequently in the fourth and fifth decades. In Kretschmer's review of forty-two collected cases in which the age was stated, thirty-six cases occurred after thirty years of age. The youngest patient was sixteen months old (reported by Albarran and Imbert). In our series, the youngest patient was three years of age and the oldest seventy-nine. The age incidence in our series was as follows:

Age	*Number of Cases*
3 years	1
24 years	1
40-50 years	3
51-60 years	1
61-70 years	2
71-80 years	2

91

Sex Incidence.— Of the cases reviewed by O'Neil[23] in the Massachusetts General Hospital, five occurred in men and four in women. Of those reported by Albarran and Imbert[24] thirteen occurred in men and ten in women. In Kretschmer's series of cases twenty occurred in men and twenty-two in women, and in our series eight occurred in men and two in women. In Simon's[8] series, the condition occurred twice as frequently in women as in men. It is also interesting to note that most of the women in which the condition has been present were multiparous. In Carson's[19] series of 146 collected cases, eighty-nine occurred in women, forty-one in men and in sixteen cases the sex was not stated.

Location and Size.— In six of the cases herein reported, the cyst occurred on the right kidney and in four it was found on the left, while in Kretschmer's collected series, in twenty-one cases the cyst occurred on the right and in twenty on the left kidney. Carson has found that the condition occurs more frequently on the right kidney. Solitary cysts of the kidney are usually unilateral although Cunningham and Zaccarini[25] reported the occurrence of bilateral cysts. It is well known that small cysts are frequently found on arteriosclerotic kidneys but these are not solitary cysts and should not thus be included in this discussion. In the cases reviewed by McKim and Smith the site of the cyst was as follows:

	Lower pole of kidney	Upper pole of kidney	Center of kidney
McKim and Smith	51	21	8
Kretschmer	13	11	
Higgins	7	3	

Solitary cysts may arise from the upper or lower pole, the anterior surface or the hilus of the kidney. In most of the cases reviewed herein the cyst was present on the lower pole of the kidney.

The cysts vary in size from a few centimetres in diameter to a large sac containing a litre or more of fluid. In one case in our series the cysts contained over a litre of fluid. Since the smaller cysts present no symptoms they are not found by the clinician, and only at autopsy.

Associated Pathology.— In addition to the cyst, various coexisting pathological lesions may be present. In our series a calculous pyonephrosis was present in two cases and caseous tuberculosis in one case. Cunningham reported a case of coexisting renal calculi and also a case of coexisting hypernephroma. Desno cited a case of a solitary cyst which was present in a tuberculous kidney and O'Neil[23] reported a cyst in a horseshoe kidney.

It is also interesting to note that in case VIII of our series, in addition to the large solitary cyst found in the kidney, a single cyst three centimetres in diameter, containing clear, serous fluid was found in the liver. This was the only other organ in which a cyst was found.

Etiology.— Various theories have been advanced in regard to the etiology of solitary cysts of the kidney. Cunningham[10] states that they are probably due to an obstruction in the uriniferous tubules and to the continued excretion of urine without an outlet.

Kampmeier[2] states that normally the human fœtus passes through a period which is characterized by the presence of numerous cystic renal tubules which if they persist and expand at the expense of the adjacent tissue, may cause a renal cyst. Caulk,[9] who studied a large series of these cases, stated that although some cysts may be congenital in origin, it seems evident that the majority are due to obstruction. McKim and Smith[17] believe they may be due to mechanical causes, they may be of neoplastic origin, or they may be congenital.

Symptomatology.— Solitary cysts of the kidney do not present any pathognomonic symptoms until they attain sufficient size to produce pressure or until they become palpable. The patient may complain of vague abdominal discomfort, and a sense of fulness, or pain in the region of the kidney. Constipation may be present and urinary symptoms may be entirely absent. Hæmaturia is a rare symptom but it has occurred in cases cited by Caulk,[9] Cunningham[10] and O'Neil.[23] In our series, hæmaturia was present in one case but this was believed to be due to congestion and enlargement of the prostate. In another case, the patient had had severe attacks of renal colic which were undoubtedly due to the coexisting real calculi. In a third case marked urinary frequency and dysuria, pyuria and hæmaturia were present but these symptoms were explained by the presence of coexisting renal tuberculosis. Frequently the presence of the tumor is noted by the patient, as in the cases cited by Cunningham,[10] Kretschmer,[2] Blanchard[11] and in one of the cases cited in this paper.

Diagnosis.— Often the condition is not diagnosed prior to operation. Bugbee[26] recently made a pre-operative diagnosis of a solitary cyst in the case of palpable tumor of the kidney. The cystoscopic examination and the functional tests gave normal findings. In two of our cases a correct diagnosis was made prior to operation. The presence of hydrops of the gall-bladder, an ovarian cyst or a tumor of the kidney may cause confusion in making a diagnosis. Lesions of the gastro-intestinal tract, however, can be

identified by a complete rontgenographic examination, and chole-cystography may be used to eliminate the presence of patholgical conditions of the gall-bladder.

Fig. 10 — Roentgenogram showing pressure deformity of stomach and duodenum due to solitary cyst of kidney.

The roentgenogram may show the outline of the cyst, especially if it arises from the lower pole of the kidney, but cysts of the upper pole are less readily visualized. The margin of the cyst is continuous with the kidney and there may be a difference in density between the cyst and the kidney. A cyst of the upper pole may attain to such a size that its weight forces the kidney downward, producing ectopia, or the ureter may be displaced from its normal position by

the presence of a cyst on the kidney. A gastro-intestinal study may disclose displacement of the colon, stomach or duodenum by the cyst as was noted in one case in this series (fig. 10).
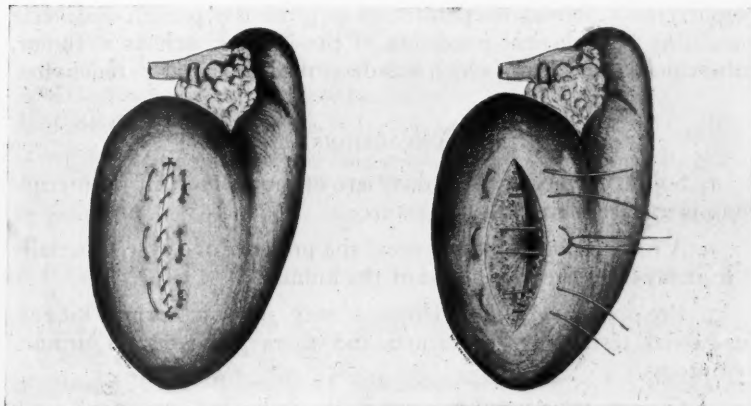

Fig. 11 — Drawing illustrating closure of kidney after removal of cyst.

As the cysts do not communicate with the pelvis or calyces of the kidney the pyelogram may be normal but if the cyst attains sufficient size to bulge into the pelvis a deformity may be shown. The findings from the pyelogram therefore depend upon the size of the cyst, its origin, and the direction in which it grows. In three cases cited by Kretschmer one pyelogram was normal and two were definitely abnormal. Urinalysis and functional tests of the kidney usually give normal findings.

Treatment.— Conservative renal surgery is especially applicable in the treatment of this pathological condition. The extraperitoneal approach naturally is preferable as adequate exposure can thus be secured. It must be remembered that the wall of the cyst is independent of the kidney capsule although adherent to it. In some cases the cyst can be successfully dissected from the kidney without removing a wedge of kidney tissue, as was accomplished in one case of our series. This is certainly the procedure of choice.

It may be necessary to resect a small wedge of kidney tissue along with the cyst in order to remove all the secreting surface of the cyst (Fig. 11). By an adequate kidney incision an excellent exposure is secured, hæmostasis being controlled by holding the kidney pedicle between the fingers. By releasing pressure upon the pedicle of the kidney spurting blood-vessels may be seen and

controlled by catgut sutures. Reapproximation of the wedge-shaped margin of the kidney is accomplished with chromic catgut mattress sutures. Any fatty tissue in the immediate vicinity is then sutured over the incision in the kidney which has been sutured. Nephrectomy should be performed only in the presence of some coexisting pathological condition of the kidney such as a tumor, tuberculosis, or calculi, which has destroyed the renal parenchyma.

Conclusions

1. Solitary cysts of the kidney are of more frequent occurrence than is apparent from the literature.

2. A roentgenogram may reveal the presence of a cyst, especially if it arises from the lower pole of the kidney.

3. Pre-operatively, a pyelogram may show a normal kidney, functional tests may be normal and there may be no urinary symptoms.

4. Conservative renal surgery is the indicated treatment for a solitary cyst, either by dissection of the cyst away from the kidney tissue or by the removal of the cyst together with a small wedge-shaped portion of the pole of the kidney. This will then allow adequate approximation of the kidney tissue.

5. Nephrectomy should be performed only in the presence of some coexisting renal pathological condition, such as a tumor, tuberculosis, or calculi, if deemed advisable.

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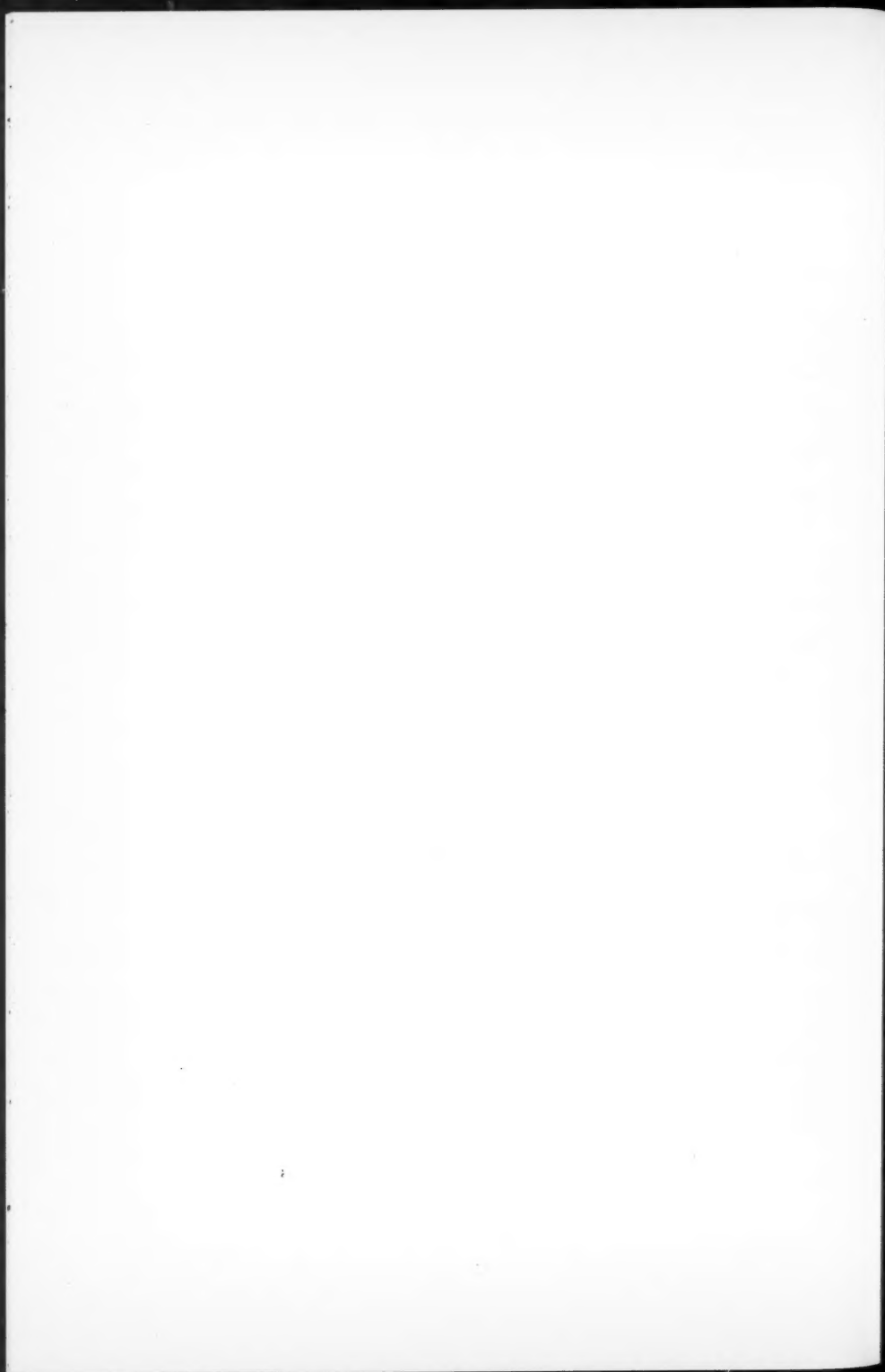
RECENT ADVANCES IN THE TREATMENT OF PEPTIC ULCER

John Tucker

A survey of the literature dealing with recent advances in the treatment of peptic ulcer reveals a growing appreciation of the importance of the pathological physiology of this malady. In the various clinics and medical centers the gastro-enterologists are forsaking "rule of thumb" treatment and are attempting to individualize each case. The effect is that an ulcer patient is receiving more intelligent treatment than the mere prescribing of a diet and alkaline powders. Physicians are growing sensible to the fact that the most important therapeutic effort is not merely to assist in the *immediate healing* of the ulcer, but as far as possible, to prevent a *recurrence* of this lesion at a future date. It is well known that one of the most characteristic features of a peptic ulcer is its periodicity, its tendency to recur most commonly in the spring and fall of the year, often with almost symptomless remissions between these semi-yearly exacerbations of indigestion. Any treatment which fails to take into consideration these fairly rhythmic periods of reactivation will, in most instances, fail to be more than a palliative. With these facts in mind, it is the thesis of this paper to elaborate the following points: (1) the known etiological factors in the production of peptic ulcer; (2) the pathological physiology of the stomach and duodenum in ulcer cases; (3) the role of diet and drugs in the effort to restore normal function; and (4) procedures to adopt in the effort to prevent recurrence of an ulcer.

I. Etiology

Knowledge concerning the cause of peptic ulcer is far from conclusive. There are theories based upon suggestive evidence, but relatively few proven facts. This may be due to the fact that experimental duodenal ulcers can be produced so easily in laboratory animals and under conditions which do not always reproduce the probable causes in man.

When one considers the ulcer itself, it becomes apparent that the disease process is, in most instances, localized to the immediate vicinity of the ulcer. The sharply circumscribed lesion or lesions are characteristic of infarcted areas, as if a terminal or near terminal arteriole had become occluded. Thus as a result of infarction, a coin-shaped area of devitalized tissue is subject to auto-digestion by pepsin in the presence of free hydrochloric acid. This seems to me the only plausible explanation for the type of ulcer which is seen at autopsy.

The auto-digestion theory is substantiated by the fact that there has been no authentic report of the occurrence of acute peptic ulcer in the absence of free hydrochloric acid. No case of acute ulcer has been shown to develop, for instance, in a case of pernicious anemia. On the other hand Kapsinow and also Berg and Jobling have produced duodenal ulcers in dogs by diverting the flow from the common bile duct away from the duodenum. Thus the alkalinity of the duodenal contents is lowered, and the acid chyme, in passing through the pylorus, fails to be neutralized satisfactorily. This leads to the attractive theory that, in man, when there is a chronic cholangeitis, cholecystitis, or chronic pancreatitis, a lowered duodenal alkalinity plus duodenitis may prepare the mucosa for the rapid formation of a duodenal ulcer through chemical changes in the duodenal lumen.

If one of the steps necessary to the production of a gastric or duodenal ulcer is an infarction in the mucous membrane, it is obvious that this must be due to an arterial thrombus secondary to an embolus or a spasm, or to an ischemia produced by a localized lymphangitis.

Rosenow has carried out some of the most notable experiments on metastatic, embolic infection by streptococci. He has been able to produce ulcers in rabbits, by the intravenous injection of streptococci obtained from the infected teeth and tonsils of patients with peptic ulcer. Also, lesions of less severity have been produced by by injecting dead bacteria or filtrates of active cultures. The results of this work have been confirmed by Haden and Bohan.

Another avenue of transmission of infecting organisms to the gastric and duodenal mucosa has been suggested and advocated by Moynihan. He believed that in as many as 66 per cent of his patients who had had operations for ulcer, there had been an associated appendicitis. By injecting the lymphatics in cadavers he was able to trace the lymphatic channels from the appendix to the pancreatic area. As the result of his studies, he believed that there was a direct route for the extension of infection from the appendix to the duodenum and stomach. Contrary to this opinion of Sir Berkeley, however, Walton was able to find evidence for a pre-existing appendicitis in only 4 per cent of his cases. In my own experience, I have found, not infrequently, the association of gall stones, or chronic appendicitis with acute or chronic peptic ulcer. That this may be more than a coincidence is attested by the fact that in two such cases the removal of an infected appendix caused a subsidence of ulcer symptoms for a period of more than two years. Yet, in many other instances, appendectomy has not cured the

ulcer, nor prevented its recurrence. I am quite convinced that the appendix and gall bladder must be regarded as possible foci of infection with but very little greater tendency to produce peptic ulcer than infection from the teeth, tonsils, prostate or cervix uteri.

There is much doubt in the minds of investigators, that swallowed pathogenic bacteria can produce peptic ulcer. Even though streptococci have been demonstrated in the crater and granulation tissue bordering the ulcers, as yet there is no proof that these come from the mouth. The most logical pathway would seem to be the blood stream or lymphatics.

It is well known, too, that severe toxaemia may be accompanied by the appearance of a peptic ulcer such as production of a duodenal ulcer after a severe burn.

Let me repeat my firm belief that a peptic ulcer will develop only if there has been a previous local devitalization of tissue by interference with the blood supply, and a secondary autodigestion by pepsin in the presence of free hydrochloric acid. I attach little importance to any principle of local trophic disturbance through a disorder of the gastric nerves save as this might influence the local blood supply. If there is any analogy between the formation of aphthous ulcers in the mouth and of peptic ulcers, it must operate through modifications in the vascular supply.

The second important factor in the development of ulcer lies, I believe, in the constitutional make-up of the patient. There appears to be a distinct type of individual who may develop a duodenal ulcer. The man with the *duodenal ulcer* diathesis is of the high-tension type, energetic, mentally alert, and nervous. He works hard, eats rapidly and relaxes little. He is short chested, rather stocky, athletic in tastes. His stomach lies in a high position, it is hypertonic and hypermotile. He is often spoken of as the human dynamo, the life of the party. The patient with *gastric ulcer*, however, falls more often into the enteroptotic group. He has a relaxed hypotonic stomach, he fatigues readily and is slowed in his reactions. There is no satisfactory explanation for these two different physiological panels. However, these two predisposing types do exist and the necessity of modifying the life of such persons according to their type must be taken into consideration when individual treatment is advised. I would not presume to imply that patients with enteroptosis may not have duodenal ulcers, or that the hyperkinetic individual who perhaps is the president of the Rotary Club, may not develop an ulcer on the lesser curvature of the stomach. However, the statements I have made concerning predisposition to the two types of ulcer, usually hold true.

From the foregoing brief remarks it can be realized that the living habits of the patient are closely linked with his constitutional make-up. Over-fatigue, when brought about repeatedly, acts by lowering general bodily resistance and thus a latent ulcer may become full-blown; excessive use of tobacco may act, as Langley has shown experimentally, by paralyzing the synapses of the sympathetic nervous system. Thus, the effect of excessive smoking may bring about over-activity of the vagi, accompanied by hypersecretion and hypermotility. A large number of patients who develop a duodenal ulcer are excessive users of tobacco.

The significance of this high-tension, dynamic, manic type of constitution in preparing the ground for the development of a peptic ulcer will be elaborated in the next section of this paper.

II. The Pathological Physiology of the Stomach and Duodenum in Cases of Peptic Ulcer

The two most important normal physiological functions of the stomach are secretion and motility. In ulcer patients these modalities are disturbed. The secretory imbalance is revealed by means of the gastric tube with the finding of hypersecretion and a high level of free hydrochloric acid. In roentgen-ray studies disturbances in motility are demonstrated, by hyperperistalsis and pylorospasm. These two factors appear to be the exciting causes of ulcer pain, as well as to interfere with the rapid healing of the damaged mucosa. I believe that I am in accord with most of the students of gastro-enterology when I assert that the presence of free hydrochloric acid is necessary for the production of pain. A possible exception might occur in certain varieties of penetrating ulcer when the pain may arise from a local peritonitis or the involvement of adjacent structures. The common use of alkalies as well as the recent use of mucin are therapeutic efforts to neutralize the acid, or to lessen its contact with the ulcerated area.

For several years I have felt that much of the discomfort associated with peptic ulcer, and especially with duodenal ulcer, is due to pylorospasm. This works in two ways: first, by contributing, with the peristaltic waves, to increased intragastric tone; and second, by preventing the normal neutralization of acid chyme which occurs when the bile-stained duodenal contents are regurgitated through the pylorus into the stomach. A second effort in therapy, then, is to influence pyloric relaxation and diminish peristalsis by the use of atropin, and its derivatives, and possibly of other drugs. In my experience, the control of the gastric tone and of pylorospasm is of much greater significance in giving symptom-

atic relief than is the inhibition or neutralization of hydrochloric acid. However, the best results come with the use of both methods.

So far I have carefully refrained from using the terms vagotonia or sympatheticotonia. While medication used to depress the vagus activity gives most satisfactory results, I still believe that the best term to use in this connection is simply disturbance in the autonomic nervous system. In this way one remains noncommittal. One can easily conceive that hyperepinephrinemia produces arteriolar spasm through the sympathetics, and that an accompanying vagotonia can produce muscular unrest in the whole gastrointestinal system.

III. The Role of Diet and Drugs in the Effort to Restore Normal Function

The following outline of management includes some of the methods used in the treatment of ulcer cases. I have summarized the therapy in a graphic form so that I can simplify my discussion.

A — Medical Management (Simple Ulcers)

Rest in Bed Diet	Modification of Living Habits		Ambulatory treatment
Lenhartz	1. Dietary	Regularity	Diet
Sippey		Calmness	Smooth diet
Smithies		Vitamins	Extra Cream
Coleman			
Leube	2. Work	Tension at work	
Others		Dissatisfaction	
		Worry	
	3. Social and Habits	Loss of sleep	
		Alcohol	
		Tobacco	
		Sex	
	4. Relaxation	Vacations	
		Midday rest	
		Hobbies	

Medication
Olive oil
Alkalies
Atropin
Bromides
Mucin
Nitrites
Non-specific proteins
Removal of foci of infection

B — Surgical Management (Refractory Ulcers; Complications)
Gastro-enterostomy
Partial Gastrectomy
Plastic Operations

The first decision the physician must make is whether to treat his patient in bed or whether he may permit him to be up and go to work. In recent years, I have found that most of my patients, both laborers and brain workers, make more progress when allowed to be ambulatory, but with considerable modification in their normal living habits. I am thoroughly convinced that the important factor is relaxation of nerve tension and not a horizontal position of the body. A man whose children are hungry, or an executive who imagines that his business is going to the bad will not get much relaxation when treated in bed.

In looking over my records, selected at random, of ten cases of simple acute ulcer treated in this way, I find that all but two, or 80 per cent, were relieved of symptoms within ten days after treatment was begun. All of these patients, whose ages ranged between 26 and 57 years, and whose symptoms had existed from 5 months to 13 years, had simple acute ulcers, as manifested by a typical history of nervousness and repeated exacerbations of pain, high gastric acidity, and stomach lesions demonstrable by x-ray examination. I advised a simple bland diet with extra cream midway between meals and at bed time. The medication consisted in the use of olive oil, one tablespoonful before meals; an alkaline powder, three to six times a day; atropin, grains 1/100 three times a day; and the liberal use of chewing gum. With this regimen the symptomatic relief has been just as satisfactory and as lasting as in patients who have been treated by a modified Sippy routine. The ambulatory patients have adjusted themselves to a normal routine while the patients treated by means of a Sippy, or similar type of routine, still must adapt themselves to their work after the period of rest in bed. In short, I feel quite certain that the important features are not in the diet, whether it be the Sippy, Lenhartz, Smithies or what not, but rather in the living adjustments plus the simple medication used. Undoubtedly some patients will require a Sippy regimen, but I believe that these are few in number and possibly limited to those in whom the disease has been complicated by hemorrhage.

The purpose of medication in the treatment of an acute peptic ulcer is four-fold: (1) to inhibit the secretion of hydrochloric acid; (2) to partially neutralize the acid already present; (3) to relieve gastric hypermotility and pylorospasm; and (4) to protect the ulcer from contact with digestive juices.

I shall discuss these features in the order just given. The secretion of hydrochloric acid is the result of nervous or hormonal activity. It can be inhibited by the use of fats and by atropin.

With this in mind, it is my custom to administer one tablespoonful of olive oil before meals, three times a day, and to prescribe a small glass of one-half milk and one-half cream, midway between meals, and at bed time. The atropin is given in doses of grains 1/100 two or three times a day.

The second purpose of medication, partially to neutralize acid already formed, is best accomplished by antacids. The use of alkalies in the treatment of incipient, acute or chronic ulcers is therefore a logical therapeutic procedure. Let us now consider the neutralizing efficiency of some of the alkalies in common use.

Sodium Bicarbonate. This salt relieves ulcer pain almost immediately, because of its ability to neutralize hydrochloric acid very rapidly, and also because of the distension effect upon the stomach by the formation of carbon dioxide. Both of these effects relieve, for a time, pylorospasm and gastric hypermotility. However, the chief objection to this alkali is that sodium bicarbonate has the peculiar property of stimulating a great secretion of gastric juice after neutralization is completed. Then too, if ulcers are near the perforation point the distension caused by the carbon dioxide gas, may facilitate perforation. This alkali should only be used when other forms of treatment have failed to relieve pain. In such instances, it should be given very much diluted and at half hourly intervals, to neutralize the acid as rapidly as it is formed. However, the use of bicarbonate of soda in the treatment of peptic ulcer should be avoided if possible.

Magnesium Oxide. This is a more desirable alkali to use since it has nearly four times the neutralizing power of sodium bicarbonate and, furthermore, it does not form carbon dioxide. However, it also stimulates a secondary increase in acid secretion after the initial neutralization. It has a mild laxative effect.

Calcium Carbonate. This alkali is more desirable for use in ulcer than either sodium bicarbonate or magnesium oxide. It does not produce a secondary hypersecretion by the gastric mucosa nor is the excess of alkali absorbed into the body. Calcium carbonate passes unaltered in the feces, yet there is some increase in the alkalinity of the blood, due to the reconversion of the calcium chloride formed in the stomach to calcium carbonate in the intestine. However, this alkaline effect is considerably less than that of sodium bicarbonate. The powdered chalk, on the other hand, does form carbon dioxide in the stomach, which is an added disadvantage.

Tribasic Calcium and Magnesium Phosphates. In 1923 Greenwald pointed out that the tribasic phosphates of calcium and magnesium act as antacids in the stomach but not as systemic alkalies, since

they are excreted in the feces rather than in the urine. Other workers have found that these salts act as efficient alkalies in the treatment of ulcer, although, at times, they give less relief than sodium bicarbonate. These salts do not give rise to toxic symptoms nor any elevation in the blood urea. By regulating the relative proportion of the calcium and the magnesium salt, diarrhea can be prevented. Their neutralizing strength is about one-half that of an equal weight of sodium bicarbonate.

Sodium and Potassium Citrate are also efficient alkalies and can be added to milk without the loss of neutralizing power.

With regard to alkalosis, I should like to say a few words. This condition is most likely to develop in patients who have renal insufficiency as manifested by a high non-protein nitrogen of the blood, or who have pyloric obstruction with resultant vomiting. The use of *sodium bicarbonate* or of *calcium carbonate* which effect the pH of the blood, should be avoided in such patients.

Symptoms of alkalosis usually develop within the first two weeks of treatment. The early symptoms are loss of appetite, irritability, dry mouth, headaches, dry skin, muscular soreness and finally nausea and vomiting. In our experience at the Cleveland Clinic any such symptoms have been of a mild type and have cleared up with reduction in the amount of alkali taken. It is best, with such patients, to use only the tribasic phosphates.

The use of bismuth salts in the treatment of peptic ulcer has a long history. However, recent work has shown that it is valueless either to neutralize acid or to coat over the ulcer crater. It has the added disadvantage of producing a black stool which might be taken for melena.

To summarize the discussion on alkalies, it appears that the most satisfactory alkalies for use in the treatment of peptic ulcer in the order of their importance are the following: (1) tribasic phosphates of calcium and magnesium; (2) calcium carbonate; (3) sodium and potassium citrate; (4) oxide of magnesia; and (5) sodium bicarbonate.

One may inquire whether or not it may be possible to lessen gastric secretion before neutralization is attempted. Pavlov showed in 1914 that olive oil diminishes the secretion of gastric juice. This is most likely brought about by inhibiting the gastric secretory factor as well as by producing a delay in evacuation of the stomach. Thus, in the absence of pylorospasm or obstruction, there is a greater tendency for the alkaline duodenal contents to be regurgitated into the stomach. Cream and sweet butter, undoubtedly, act in a similar manner and have the added advantage of being food

rich in calories. I have already outlined the method of using olive oil before meals and cream midway between feedings. The third reason for the use of medication in the treatment of peptic ulcer is to prevent hyperperistalsis and pylorospasm. It is very important to overcome this physiological imbalance, or else the unfavorable symptoms may be prolonged or healing may be delayed. Pylorospasm increases discomfort or pain, it prevents the normal regurgitation of alkaline bile and pancreatic juice into the stomach and also prevents the gastric secretion from passing into the small intestine. With pylorospasm there is an increase in the number of peristaltic waves in the gastric wall, so that this organ is writhing and churning with unusual activity. This fact may be substantiated clinically, for I have been able to relieve pain in several cases of chronic duodenal ulcer by the use of atropin alone. I prefer to use atropin or its less toxic derivative, novatropin, rather than the tincture of belladonna, since the latter may have variable strength. Atropin inhibits gastric secretion in the same manner that it inhibits motility, by affecting the nerve endings of the vagi.

Thus it is that if the secretory or motor functions of the stomach can be controlled the symptoms in uncomplicated ulcer cases can be relieved.

Of the recent advances in ulcer therapy, perhaps the most promising is that advocated by S. J. Fogelson. Basing his treatment on the physiological observations of Heidenhain, of Pavlov, and of Ivy and Kim, he suggested that gastric mucus was an ideal antacid in that (a) it combines readily with free acid; (b) it is a natural substance which plays normally a protective, soothing and lubricating rule in the function of mucous membranes; and (c) its secretion or ingestion causes no chemical disturbances in the body and no unfavorable effect on gastro-intestinal secretory or motor activity."

Using powdered mucin, prepared by Armour & Company, he found that one gram combines with 1 c.c. of 0.5 per cent hydrochloric acid. In his chemical experiments, he used one ounce of powdered mucin with each meal and 20 to 40 grains in tablet form at intervals of one-half to one hour, when the patient had severe pain, or when the gastric contents after an Ewald test meal showed an unusually high level of free acid. He found that the symptoms disappeared after three days of treatment and there was continuous absence of pain. He believes that there are two factors involved in the relief, namely: (1) protective coating of the ulcer, and (2) neutralization of free hydrochloric acid and delaying the progress of pepsin through the layer of mucin. With this work in mind, one must agree with the chicle manufacturers, that to chew gum aids digestion.

Among the more recent forms of treatment for ulcer is that of protein shock. Meyer and Kartoon used the intravenous injection of foreign protein in the treatment of peptic ulcer. Their conclusions were as follows: (1) Relief from pain during treatment for peptic ulcer by injection of foreign protein is independent of changes in acidity. (2) Diminution in gastric tonus and contractions are important factors in the relief from pain. (3) Increase in vascularity in the capillary bed in and about the ulcer is an important factor. (4) Non-specific protein therapy is only an adjunct in the treatment of peptic ulcer.

Parathormone has been used in the treatment of peptic ulcer in doses of 2 to 3 units daily, on the basis of its ability to reduce muscle tone. However, the advocate of this treatment used also atropin sulphate in doses of 1/100 grain, which of course vitiated his results, for as stated above, atropin itself will relieve the pain.

Very recently Beams and Barlow have shown that the use of nitrites in the form of amyl nitrite, nitroglycerin, and sodium nitrite were very efficient antispasmodics. These drugs were used experimentally during fluoroscopic observation of the gastro-intestinal tract. The conclusions drawn from this study were as follows: (1) The effect of nitrites on abdominal pain arising from the gastro-intestinal tract was observed in sixty patients. All of the patients without organic lesions were relieved by the nitrites. (2) Evidence has been offered which indicates that relief from pain by the nitrites is dependent on cessation of peristalsis and diminution in tone. The failure to obtain relief is probably due to the inability of the muscles to relax. (3) Of 200 patients observed in the fluorscopic studies only ten failed to show cessation of peristalsis and diminution of tone in the stomach and intestines following the use of nitrites. (4) Nitrites have been found to be a great aid in differentiating organic deformities from functional ones. (5) The antispasmodic action of nitrites is to be preferred to that of atropin, but neither is wholly satisfactory.

This work by Beams and Barlow suggests the advisability of giving physiological doses of nitrites in those cases of painful ulcer in which atropin has failed to give relief or in which atropin is not well tolerated. I have not had an occasion, as yet, to use this drug.

The treatment of uncomplicated peptic ulcer has many features in common with diabetes. In both disease, the living habits of the patient have been faulty, they have eaten improperly; high nervous tension has been a common feature; both diseases are chronic, both tend to recurrences; both may develop serious complications, and both require dietary regulation. In peptic ulcer, as in diabetes,

the patient must be instructed in the main features of the disease so that he can cooperate intelligently with the physician. There is no reason why an ulcer clinic should not be as important in the establishing of proper treatment of peptic ulcer as similar clinics are in the treatment of hyperglycemia.

Therefore, our therapy must begin by a better regulation of the patient's living habits. He must be told that the use of tobacco, in any form, must be discontinued until the ulcer is healed, that the surreptitious use of tobacco is a greater sin than the stealing of his neighbor's purse. He must shun Bacchus to the possible sacrifice of conviviality. He must substitute milk for Madeira, water for wine. Then too, it is important for him to retire sufficiently early to get nine hours of sleep at night, and he must rest during the day, particularly after meals. All of this may require a complete "about face" in his habits of living. If his friends can not sympathize with this complete conversion in his life, then he should seek those who live at a more sane level. Let such a patient eat more slowly and more regularly, let him follow with fidelity the diet list and medication prescribed. Such virtue will be rewarded.

Treatment of an acutely bleeding ulcer. The patient should be put to bed at once. If there is vomiting of blood or melena, morphine sulphate, grains 1/6, with atropin sulphate grains 1/100 should be given by hypo. He should be starved until all bleeding has ceased for at least forty-eight hours. An empty stomach is less likely to bleed. If bleeding will not cease, blood clots can be evacuated from the stomach by the careful use of a stomach tube. The lavage fluid may consist of ice cold water, four to six ounces, and the washing is repeated until the water is free of blood. If this is insufficient, the washing fluid may consist of iced 1/1000 ferric chloride solution, followed by the instillation of drachms one of 1/1000 solution of epinephrine.

Blood transfusions are indicated if the hemoglobin falls to 40 or 50 per cent. Fluid can be given by Murphy drip — using 5 per cent glucose in physiological sodium chloride solution. A similar solution can be used intravenously. A surgeon should always see the patient in consultation, for, if all of these measures fail, operation will be required. Occasionally, in spite of all care and even though repeated transfusions have been used, the patient will continue to bleed and finally die. Hence, these cases are emergency problems and should be watched with great care and attention.

How is the physician to know when an acute ulcer is healed? This is a difficult matter to establish with certainty. The presumptive evidence of a healed ulcer is cessation of pain, tenderness or

rigidity; the absence of occult blood in the stools and x-ray evidence for healing. In *gastric ulcers*, Hurst and Stewart advocate x-ray examination at the end of two or three weeks of treatment and then at weekly intervals until the crater is reduced to a minimum or until the deformity has disappeared. Where the deformity remains unchanged and occult blood persists in the stools, operation is advocated on the basis that the ulcer may be malignant.

If all evidence indicates that the ulcer has healed it is still important to keep the patient on a limited diet and under regular periods of observation for the ulcer diathesis is still present.

I shall deal very briefly with surgical treatment in peptic ulcer. The well established indications for surgical intervention are as follows: (1) intractable ulcer, (2) carcinoma suspect, (3) pyloric obstruction, (4) recurrent hemorrhage, and (5) perforation.

I should like to emphasize that pyloric obstruction with retention should have the advantage of medical treatment before an operation is performed. I believe that roentgenologists will agree with me that they have no certain method of determining whether the obstruction is due to stricture, spasm or edema. The use of atropin as a differentiating method has proven disappointing. Even if a carcinoma is suspected, especially when free hydrochloric acid is present in the stomach, there is no particular harm to be done by giving the patient two weeks of medical treatment followed by a second x-ray study. To quote Frank H. Lahey, "with increasing experience with ulcer, I have learned that pyloric obstruction occurring with active ulcer symptoms is most commonly due to spasm, infection and edema and that a large majority of such patients can be relieved of their obstruction by non-operative measures, rest, diet and neutralization, and that surgery is much less frequently indicated."

I wish to emphasize the importance of having a surgeon see all patients in whom hemorrhage is present or in whom perforation or organic pyloric obstruction is suspected. It will be much easier for him to have a complete picture of the case, should emergency operation be required.

SUMMARY

In the modern treatment of peptic ulcer we attempt to accomplish three things: (1) relief of the symptoms, (2) healing of the ulcer, and (3) prevention of recurrence. To attain these ends it must be realized first that there is such an entity as a constitution predisposed to ulcer. With this in mind, an attempt is made to modify the patient's living habits and to regulate his life even after

the acute ulcer has healed. Diets, alkalies, atropin and olive oil or other fats also are prescribed. In addition prompt surgical intervention must be afforded the patient when the proper indications are present. After the operation, the internist must again assume the responsibility of treatment.

I believe that our success will be directly proportional to the care with which patients are educated in a knowledge of their disease, and are thus influenced to give the physician their willing cooperation. The medical profession is as yet in a maze of uncertainty about ulcer. It is to be hoped that further knowledge of the factor of focal infection or the new attack of adrenal denervation, such as is being pioneered by Doctor Crile, may help to lead us out of the wilderness.

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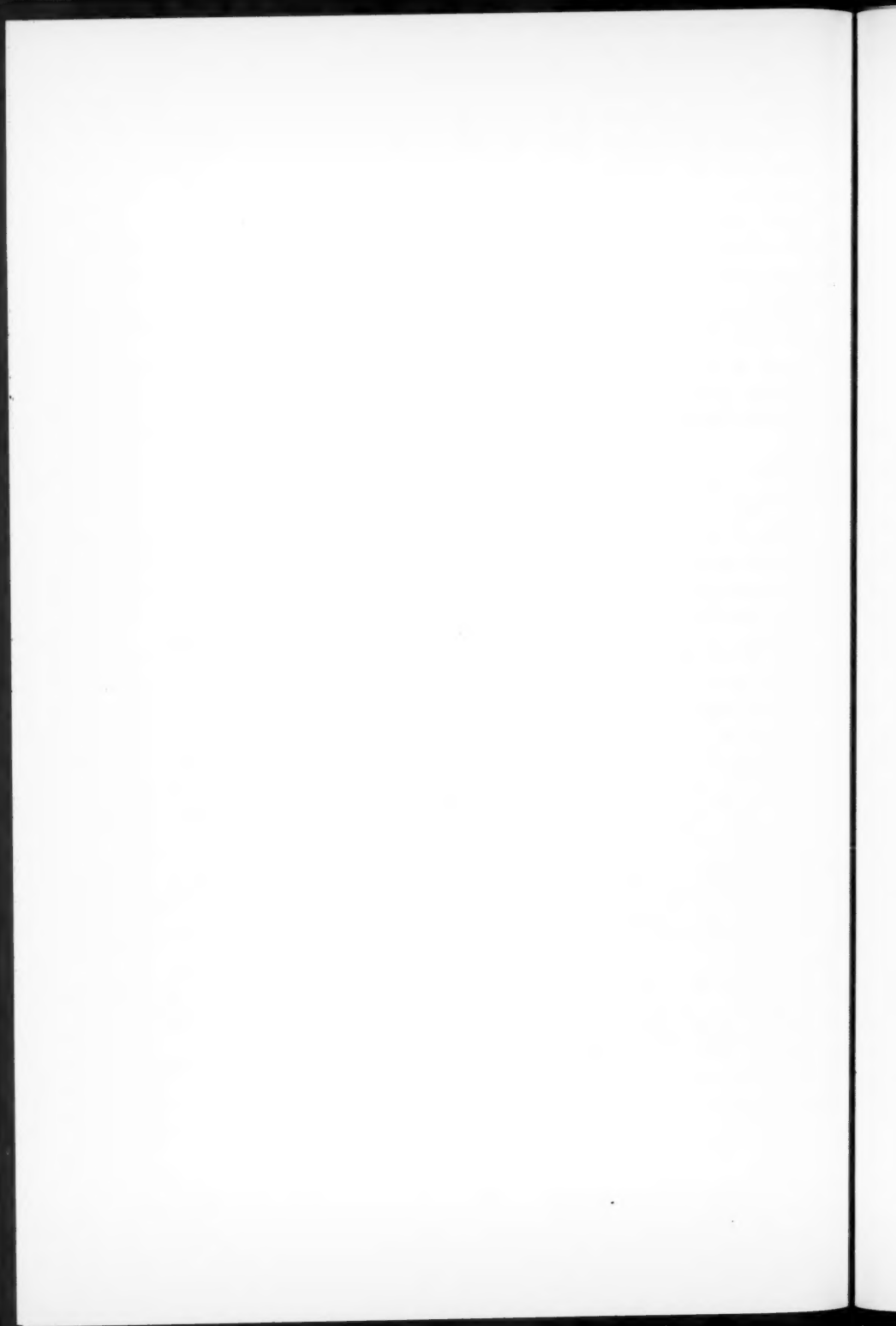
A CASE OF THALLIUM POISONING FOLLOWING THE PROLONGED USE OF A DEPILATORY CREAM

Wallace S. Duncan, M.D., and Edward H. Crosby, M.D.

The Journal of the A. M. A. recently published an article[1] bringing to the attention of the medical profession the sale of a depilatory cream which was found to be particularly high in thallium acetate content. This article led to the correct diagnosis in the following case:

Report of Case

A white woman, aged 24, came to the Cleveland Clinic complaining of severe pain over the soles of both feet and ankles, weakness of both feet and legs, and intense burning of both feet, most marked in the third, fourth and fifth toes. She had been receiving treatment elsewhere for arthritis of both feet and ankles.

Four and one-half months prior to entering the clinic, the patient had first noticed intermittent epigastric pains which gradually increased in severity to sharp, cramplike pains throughout the entire abdomen. These pains were associated with nausea, several attacks of vomiting, loss of appetite and substernal pain, but were unrelated to the taking of food. Two months after the onset, the abdominal pain subsided and the patient first noticed burning and numbness of the third, fourth and fifth toes of both feet. The onset of this numbness and burning was insidious and at first was apparent only while the patient was bathing. As the numbness increased and the burning became intense and almost constant there developed an increased sensitivity of the skin over the soles of both feet, the outer three toes, the dorsum of the feet, and the anterior surfaces of the ankles and legs, extending to the knees. Weakness was then noticed in the third, fourth and fifth toes gradually extending to include the muscles of the calves and the thighs. During the three weeks preceding her examination at the clinic, these symptoms were so severe that the pressure of the bedclothes caused pain, and walking was almost impossible. Several dizzy spells were experienced and at times the vision was blurred. The patient had become very nervous, cried easily, had lost about 10 pounds (4.5 Kg.) and felt continually tired.

The past history revealed the following facts: The patient had used alcohol for a period of time, the amount, however, having been greatly reduced in the preceding year and a half; cigarets had been used somewhat in excess, from twenty-five to thirty in a day, and for several years she had used a henna rinse after washing her hair.

The family history revealed nothing relevant to the existing condition. The menstrual history was significant in that the last period had occurred seven weeks previous to examination.

Physical examination revealed undernourishment, apprehension and emotional instability. The temperature, pulse, respiration, and blood pressure were within normal limits. The hair was definitely henna-colored but firmly embedded. Hair was distributed normally over the body with the exception of the face, where the growth was more profuse than is normal and this hair was firmly embedded. The pupils were equal and reacted to light and in accommodation. Ophthalmoscopic examination showed that the fundi were entirely within normal limits. The ears and the nose were normal. The tonsils had been removed and no fragments remained. No pathologic condition was found that would account for the patient's dizziness. The tongue was heavily coated; it protruded in the midline and a fine tremor was present. The teeth were in good repair but there was infection of the gums, particularly about the lower incisors. The thyroid gland and the lymph glands showed no enlargement. The breasts were small and firm, and a small amount of colostrum could be expressed. The lungs and heart were normal. The abdomen was flat and symmetrical, and tenderness was present throughout on deep palpation. The pelvic examination showed the vaginal mucous membranes to be slightly blue in appearance, the cervix soft, the fundus enlarged posteriorly, and uterine arteries definitely palpable. The upper extremities were normal. The lower extremities were of equal length. There was obvious muscular atrophy of the thigh and calf group of muscles, which was slightly more marked on the left side. A moderate degree of bilateral drop foot was present associated with marked weakness with complete inability to move the three lateral toes on either lower extremity. Heat and cold were readily distinguished by the patient over all areas of the body. Touch and pain sense perceptions were markedly increased over the outer surface of each calf, the lateral surface of the feet including the third, fourth and fifth toes, and the soles of the feet. Touch and pain were less readily appreciated over the medial surface of each calf. All reflexes could be readily elicited. The knee jerks were hyperactive; the Babinski test was not elicited. No rombergism was present. Movement of the lower extremities was painful, probably because of increased skin and muscle sensitivity. There was no evidence of joint reaction apart from some thickening about the metatarsophalangeal joints. Heat could not be tolerated on either lower extremity. All the other joints were normal.

The urine was normal except for an occasional pus cell. The red blood cells numbered 3,875,000 per cubic millimeter, the white blood cells 10,750 per cubic millimeter, hemoglobin 78 per cent (Tallqvist), polymorphonuclear neutrophils 76 per cent, small lymphocytes 23 per cent, transitionals 1 per cent. The phenol-sulphonphthalein return was within normal limits; blood calcium, sugar, and urea were within normal limits; the Wassermann reaction was negative. A blood smear stained with Wright's stain showed nothing abnormal. Flame and spectroscopic examination of a twenty-four hour specimen of urine showed the presence of a small amount of thallium.

The temperature about both feet, recorded with a skin thermometer, is given in the accompanying table. The normal temperature with this thermometer is from 32° to 33° C.

Temperature of the Toes

	Left Foot, Degrees Centigrade	Right Foot, Degrees Centigrade
First toe	34.8	34.4
Second toe	33.8	34.7
Third toe	35.0	35.9
Fourth toe	36.3	36.2
Fifth toe	37.8	35.9

Galvanic and faradic stimulation over the muscles of each lower extremity gave no response. Only with currents higher than normal could a response be obtained when the external popliteal and anterior tibial nerves were stimulated.

The patient was admitted to the Cleveland Clinic Hospital with a diagnosis of peripheral neuritis of obscure origin, associated with early pregnancy. After admission, it was discovered on further questioning of the patient that she had been using a depilatory cream, "Koremlu," nightly for the preceding five months, beginning its use two weeks before the appearance of the first symptoms. A quantity sufficient only to cover the upper lip and the chin had been used on each occasion. At each application the cream was well rubbed in.

Careful questioning revealed the fact that a henna hair rinse had been used every four months for the preceding five years. Henna is a harmless vegetable, but in the manufacture of hair dyes and washes either a salt of some one of the heavy metals or a coal tar product is added. Although these materials are toxic, it is scarcely

possible that the existing neuritis could be traced to the dye, which was used at such infrequent intervals. Alcohol had been used for the preceding six years but only in very moderate quantity during the preceding year and a half and the alcohol had been analyzed prior to its consumption. From twenty to twenty-five cigarets had been used daily over a period of months, but this obviously could not account for the condition. It was therefore concluded that the peripheral neuritis was most logically attributable to the toxic effects of thallium absorbed from the depilatory cream.

There was no doubt concerning the diagnosis of pregnancy and the question immediately arose as to the advisability of a therapeutic abortion. There were three excellent reasons why a therapeutic abortion should be induced:

1. In thallium poisoning the ductless glands are especially involved. Dixon[2] has produced cretinism experimentally in young animals by chronic poisoning with thallium, probably by its action on the thyroid gland.

2. In thallium poisoning the kidneys are temporarily damaged, producing albuminuria. Although the patient showed no kidney damage, the added burden of pregnancy increased the probability of interference with kidney function.

3. The mild toxicity associated with pregnancy would be an added hazard to the recovery from a condition in which the prognosis could not be definitely determined.

Following consultation, therefore, it was considered advisable to induce abortion and an attempt was made by the use of theelin and oxytocin in the following manner:

At 8 p.m. the patient was given 2 cc. (100 units) of theelin, subcutaneously. At 8 a.m. the following morning she was again given 2 cc. At noon she was given 3 cc.; at 4 p.m. she again received 3 cc. At 8 p.m. the dose was increased to 4 cc., and the following day she received four doses of 4 cc. each. The next morning at 8 o'clock she was given 4 cc. of theelin, and after that she was given oxytocin in four doses of 0.5 cc. each, at half hour intervals. She received a total of 34 cc. (1,700 units) of theelin and 2 cc. of oxytocin. No change was noted by rectum in the size of the external os, and no pains or abdominal discomfort were experienced by the patient. Twenty-four hours later the advisability of giving more oxytocin was considered, but owing to the fact that the urinary output was considerably reduced during these twenty-four hours, it was considered inadvisable to make any further attempt to induce abortion in this manner.

As the method described was found to be inadequate, a dilation and curettage was carried out following packing of the cervix and uterus, which had been done on the preceding day.

The patient was discharged from the hospital within a short period and since that time has shown definite improvement. She still suffers from very persistent burning in the feet, with weakness in the toes, which were affected at the time of her admission to hospital.

COMMENT

Thallium was discovered by Crookes in 1861 and investigated chemically by Lany in 1863. It was introduced into medicine about twenty years ago as a remedy for certain disorders of the skin. Thallium (atomic weight 204) belongs in the group with zinc, lead and tin. In its action it resembles potassium and arsenic rather than heavy metals and is an active poison, being slightly more toxic than arsenic and having a distinctly accumulative effect. Acute thallium poisoning is characterized by stimulation of the heart followed by depression, resulting in death from cardiac failure. Chronic thallium poisoning is characterized by injury of the endocrine glands, peripheral neuritis, and falling out of the hair even to complete alopecia. Very small doses fed to young animals cause stunted growth and symptoms of cretinism.

Thallium has been used in the treatment of syphilis, for the arrest of night sweats in phthisis, and in the treatment of cystitis. Its use, however, has been abandoned because of the toxic symptoms that it produces. Dermatologists use thallium in small doses to produce epilation in diseases of the scalp in children, and Davies and Andrews[3] showed that children up to 7 or 8 years of age withstand the action of thallium well. Older children and adults are more likely to show toxic symptoms. In one of their cases, arthritis and periarthritis of the knee joints were present.

In 1912, Sabouraud,[4] a French authority on diseases of the hair and scalp, devised an ointment of thallium acetate for use in the removal of superfluous hair. Since that time, accidents have been reported from its use. The original Sabouraud prescription called for an introduction into the ointment of not more than 1 per cent of thallium acetate and Sabouraud urged that even in this dosage it should be applied only once a day and that an amount of the ointment not larger than two kernels of wheat should be used. Ointments containing 1 per cent of thallium acetate should not be used over an extensive surface.

Dixon pointed out that thallium used experimentally in animals which had been shaved produced a rapid growth of hair. He also

reports that thallium salts exert no local action but when rubbed into the skin with oil or alcohol are rapidly absorbed and produce a systemic reaction, the effect being mainly on the autonomic motor system, which becomes more sensitive, so that electrical stimulation of the nerves produces an exaggerated response, even though the stimuli are below the normal response level.

Ormerod,[5] by postmortem analysis of body structures, showed that the muscles act as the main storehouse for thallium and that the excretion is mainly by the kidneys, but that thallium is also excreted in all the body secretions.

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TOXIC HEPATITIS DUE TO CINCHOPHEN

A REPORT OF THREE CASES

GORDON A. WINFIELD

Cinchophen or atophan (chemically 2 phenyl-quinoline 4 carboxylic acid) was first prepared by Doebner and Gieske[1] in 1887. It was introduced by Nicolaier and Dohrn[2] in 1908 for the treatment of gout. The tenth edition of the U.S.P.[3] recognizes it as cinchophen. It was generally considered that the drug was of low toxicity; Sollman[4] gives no warning against long continued massive dosage; the general practice has been to maintain saturation over long periods.

However, as early as 1913 cases of skin rashes and gastro-intestinal upsets resulting from the use of this drug were reported in the literature. [5][6] In 1922 Schroeder[7] drew attention to the toxic effects of the drug, and published a review of 17 cases in which such effects were observed. In 1927 Reichle[8] reviewed 47 cases collected from the literature among whom 11 patients had died from toxic jaundice.

Because of these toxic effects, it seems worthwhile to offer a discussion of some of the more common symptoms produced by this drug, and to present three cases of toxic hepatitis due to its use, one of which was fatal.

Cinchophen is a white powder having a sour and bitter taste. It is related chemically both to the alkaloids and acids. It is acid in reaction and forms salts with the alkali metals.[9] It has been used with excellent results in the treatment of gout and allied conditions, its action closely resembling that of the salicylates. It is also effective as an analgesic antipyretic, and promotes the excretion of uric acid by direct action on the kidneys. This last effect is thought to be due to an increased permeability of the kidney to urates, so that those previously retained in the blood because of the difficulty attending their elimination by the kidney escape in the urine.[4]

The absorption of cinchophen from the stomach occurs very promptly. Its effect on the excretion of uric acid is at its maximum about an hour after the drug has been given by mouth, the effect beginning to decline in three hours. This is a temporary effect, however, as although the excretion of uric acid is increased during the first three days of administration of the drug it then returns to normal, or below, whether administration of the drug is continued or not. For this reason many recommend that the drug be given for periods not exceeding three days, and that it then be discontinued

for at least four days. For the most part the drug appears to undergo decomposition in the tissues, although an unchanged portion is excreted in the urine.[10] Almost every case of poisoning which has been reported was the result of uninterrupted use of the drug over long periods of time.

In medicinal doses cinchophen usually causes no symptoms whatever. In very large doses it may cause a burning in the stomach which lasts only a short time.[9] The toxic action of the drug is thought to be due to the presence of the quinolin nucleus, which consists of the benzene and pyridin rings.[4] Most individuals are not susceptible to the toxic action, and toxic jaundice occurs only in the presence of an individual idiosyncrasy, which may be artificially induced. For this reason a therapeutic test of the drug before its administration has been advocated. The dosage and the duration of administration before the onset of symptoms varies with the individual case.[11] Cases of extreme toxicity have been reported following very small doses.[11] The symptoms come on abruptly, and, as a rule, appear late. Frequently they may appear some time after administration of the drug has been stopped. The amount of glycogen present in the liver is probably an important factor in the production of toxicity, there being a greater tendency to liver degeneration when this amount is small. Thus, alcoholics, pregnant women, and those who have previously suffered from liver disease associated with jaundice are more likely to suffer the toxic effects of administration of cinchophen. The route of attack is not definitely known.[11] [12]

The principal symptoms of toxicity due to cinchophen are headache, gastrointestinal disturbances, and jaundice. The most frequent of these is jaundice, which has been present in almost every reported case. Vomiting, anorexia, heartburn and diarrhoea, when present, usually precede the jaundice. On the other hand, jaundice may appear first and be intense from the beginning and it may be accompanied by diarrhoea.[13] Weakness may be noted first, and in some cases this symptom has been accompanied by emotional disturbances and loss of voice.[14] Itching of the skin is a common symptom.[15]

As a rule the first symptoms noted are pains in the right upper quadrant and right back, and vomiting. After the patient has felt ill and tired for a few days, jaundice sets in. Severe vomiting, often of a bilious nature, may be present from the outset. Sleepiness and stupor progressing to delirium frequently occur, and the patients rapidly retrogress, the majority dying in coma.

The liver may at first be enlarged, but soon begins to decrease in size until it cannot be felt. As a rule, the left lobe decreases more rapidly, and this is an important point in diagnosis. The jaundice is very rapid in its development and varies in its intensity. The spleen, although it is enlarged, can seldom be felt.

The amount of urine decreases. It is dark brown and contains traces of albumin but no sugar. Hyaline and granular casts, red blood cells and bilirubin crystals may be found. Tyrosin may be present but is not of diagnostic significance. The total nitrogen of the urine is increased, as are also the ammonia and uric acid. The duodenal contents may or may not show bile. The patients are usually constipated; the stools may be acholic and at other times may show bile. The blood shows a markedly increased bilirubin. The blood sugar is first increased and later decreased. The sugar tolerance is later decreased. Blood coagulation is decreased and the bleeding time increases early. The red blood cells and hemoglobin are usually increased, although the former may be markedly decreased. The total number of white blood cells is usually increased, but leukopenia with relative lymphocytosis may occur. The temperature is variable; there is a high rise before death.

The duration of the symptoms varies with the severity of the process. It is important to remember that these cases may present symptoms of acute gall bladder disease, and there are cases on record in which an operation has been performed.[12]

Early diagnosis is important. At the first sign of toxicity the administration of the drug should be stopped, and a careful watch kept over the patient. If urticaria occurs calcium lactate may be used. For the relief of the gastrointestinal symptoms glucose should be given in large amounts, by mouth, in the form of the Murphy Drip, or intravenously, if the symptoms are at all severe. When glucose is administered insulin should be given also in order to better fix the glycogen of the liver to protect it from further damage, and so to aid in recuperation of this organ.

The pathological picture resembles that of acute yellow atrophy. The liver is small, and the left lobe may be so atrophied as to have almost disappeared. There is almost complete necrosis of the liver cells with little or no evidence of regeneration. The bile ducts are unaffected. The kidneys are large, soft and pale. The damage is chiefly in the tubules of the cortex, and is in the nature of cloudy swelling and destruction. The glomeruli apparently escape damage, and the collecting tubules are normal. As a rule other organs are not affected, although cases have been reported in which there were

present acute splenic hyperplasia,[8] acute pancreatitis[16] and petechial hemorrhages on the mitral valves, pleura and mucous membranes of the stomach and jejunum.

During the past fourteen months three cases of toxic hepatitis due to cinchophen have been seen at the Cleveland Clinic; one of these was fatal. The case reports follow:

Case 1.— The patient, a man 45 years of age, was first seen at the Clinic on October 16, 1929. At that time he complained of pain in the left hip and back, which had been present for several months, and which was so severe as to incapacitate him. The pain had been growing worse recently, and the patient noted that it was aggravated by cold and rainy weather. At first it was worse in the evening and better in the morning, but recently the patient had noted stiffness in the joints on waking in the morning, with some limbering up on motion. The family and personal history were unimportant.

The patient was a very robust, rather obese man, weighing 210 pounds. The temperature was 98.6°, pulse 80, blood pressure 152/88. There was a scoliosis to the right in the lower two-thirds of the dorsal spine, and to the left in the lumbar spine. He moved with great difficulty. There was a marked restriction of movement in all directions in the lower back. There was marked tenderness over the right flank, at which point no masses could be discovered. There were no gross changes suggestive of polyarthritis. There were extensive varicosities over the right saphenous vein to a point two inches above the knee. There was extensive pyorrheal involvement of the teeth. The patient experienced discomfort on straight leg raising on both sides, particularly the right.

At the time of this first examination the impression was gained that the patient had a hypertrophic arthritis aggravated by his activity, and that the present acute attack was due to an injury superimposed on the arthritic process.

Examination of the nose and throat showed a deviation of the nasal septum to the left and chronic tonsillitis, indicating that the tonsils might be a focus of infection.

X-ray examination revealed a marked left lumbar and lower dorsal scoliosis with rotation, with considerable hypertrophic arthritis.

The diagnosis made at this time included scoliosis, hypertrophic arthritis of the spine, chronic tonsilitis, and pyorrhoea.

The patient was advised to rest, to apply heat to his back, to have the teeth cared for and to have tonsillectomy if no improvement resulted from these measures.

On October 21st he reported that he felt much better, but on January 6th the patient's wife reported that the symptoms had increased in severity and she was advised to bring him to the hospital.

The patient was seen on January 13th, when he stated that he had been having very persistent pain in the lower back and upper spine. He had been taking cinchophen for several days, but the exact amount administered was not known. He had had some gastrointestinal disturbance and about January 8th jaundice had developed accompanied by considerable nausea and some pain in the right upper quadrant of the abdomen.

Examination at this time showed a diffuse icterus, with a yellow-ish discoloration of the sclera. Movement in the lumbo-sacral region was markedly restricted and there was tenderness over the lower back. The liver edge was palpable and tender.

The patient was referred to the Medical Division for further investigation, and the following additional history was obtained. Six days before this visit he had had mild pain in the epigastric region, accompanied by nausea and vomiting. The skin became yellow. The urine was highly colored and the stools were pale in color. The pain lasted for some hours and then was relieved. The stools continued to be pale in color. The impression at this time — January 13th — was that there was an obstruction of the common duct or catarrhal jaundice.

The patient was admitted to hospital on this date. Further ex-amination in the hospital disclosed marked jaundice with red palms and finger tips. There were numerous telangiectases in the skin. The chest was barrel shaped with prominence on the right side posteriorly and flattening on the left side. Percussion and ausculta-tion gave normal findings. The abdomen was evenly rounded with a slightly full contour. The liver was palpable at the right costal margin and was not tender. There was some tenderness to pressure in the region of the right costal margin and also at the tip of the eighth left costal cartilage. The temperature was 99.4°, pulse 70, respiration 20, blood pressure 112/60. An x-ray examination of the gastrointestinal tract made on January 15th disclosed a non-functioning gall bladder. The serum bilirubin on the day of admis-sion was 16.7 mg. per 100 c.c. Blood count: red cells 4,370,000; white cells 5000; hemoglobin 80; polymorphonuclears 72, small lymphocytes 20, large lymphocytes 8. The urine contained albumin 1+, bile 2+, and there was an occasional hyalin and granular cast.

On January 23rd the patient's condition was about the same. The jaundice was quite deep; serum bilirubin was 22.7 Some distress was present over the chest and up into the neck. The liver was palpable, regular in outline and not tender. On January 29th the patient did not feel at all well. There was a feeling of tightness across the lower chest and axillary regions, particularly on deep inspiration. X-ray examination revealed a large, dense circum-scribed mass at the hilus in the posterior portion of the right lung, extending down behind the diaphragm. This mass had somewhat the appearance of a tumor, but the impression was that it was of an inflammatory nature, either from an old encapsulated empyema or an unresolved central pneumonia. Investigation of the genito-urinary tract on this date showed no evidence of pathology.

On February 3rd the patient was much worse. He complained of pain across the chest and up into the neck. He felt weaker and was losing weight. The diastase of the urine was at the upper limit of normal.

By February 11th the jaundice had almost disappeared (serum bilirubin 5.2) but pain was still present in the upper region of the spine. The liver edge was palpable, sharp and not tender.

In order to rule out the presence of malignancy an x-ray examina-tion of the spine was made. No definite evidence of metastasis was found but in the region of the sixth dorsal vertebra an area of rarefaction and some compression was noted. However, this find-ing is not at all characteristic of malignancy. Clinical examination of the spine failed to reveal any evidence of malignancy. The temperature remained normal throughout the stay in the hospital.

When this patient was admitted to the Clinic his condition was diagnosed as hypertrophic arthritis. There was no evidence of any gastrointestinal pathology either from the history or the physical examination. It is to be noted that gastrointestinal symptoms and jaundice did not occur until about January 8th, at which time he had been using cinchophen for several days. It is to be further noted that when administration of the drug was stopped, and the patient was put on treatment, the gastrointestinal symptoms and jaundice disappeared rapidly, until at the time the patient was discharged on February 15th the nausea, vomiting and jaundice had completely disappeared. I believe this evidence is sufficient to class this patient as a case of toxic hepatitis due to cinchophen.

After his discharge from the hospital the patient was not seen again and letters sent in an effort to determine his subsequent progress were returned unopened.

Case 2.— The patient, a woman 49 years of age, came to the Clinic on December 8, 1930, complaining of pain in the chest which had been present for the past ten years. The pain came in attacks and radiated up into the neck and down the right arm. It was not related to food or effort. At first the pain occurred only about once a month, but at the time the patient entered the Clinic it was occurring every few days and lasted from two to three days in the form of a dull ache. This pain had no connection with the bowels. Sick headache occurred sometimes but was not related to the pain in the chest. The attacks made the patient feel weak, but did not frighten her. The pain was accompanied by some belching of gas and some soreness in the upper right abdomen.

The patient's mother had died of diabetes associated with gangrene. One brother had died of an unknown internal disease.

The patient had had measles, mumps, and whooping cough and during the entire year, 1923, she had suffered from rheumatism which had cleared up before she entered the Clinic. Following an accident to her right hip an abscess had developed, which was drained in 1909.

The patient was a well-nourished, well-developed woman. The temperature was 98.2°, the pulse 88, blood pressure 120/80. Physical examination gave normal findings except for one enlarged node in the right axilla, and a little soreness in the right breast. No local tenderness was present in the right pectoral muscle, and all movements of the arm and shoulder were free.

The nose and throat examination revealed a deviated nasal septum and chronic tonsilitis, indicating a possible focus of infection.

The diagnosis was neuralgia of the chest and arms, chronic tonsilitis, deviated nasal setpum.

On December 22nd the patient was still complaining of distress in the right side of the chest which she said sometimes kept her awake. There was some belching of gas. X-ray examination of the gastrointestinal tract gave normal findings. The patient was started on cinchophen grs. 7.5 b.i.d., 30 tablets in all being administered.

On January 5th she still complained of gas which prevented her from eating much food. There was still some distress in the chest. She was given a prescription containing sodium salicylate, sodium bicarbonate, and sodium bromide and was advised to have her tonsils removed.

On January 8th while taking a bath the patient noticed a decidedly jaundiced condition. She had had no cinchophen for two

weeks. The clinical impression at this time was that catarrhal jaundice was present. She was given magnesium sulphate and advised to discontinue all other forms of medication.

On January 17th the patient was seen at home. She was comfortable, her only complaint, aside from increasing jaundice, being a poor appetite. She was mentally alert. She was advised to force fluids, and to take plenty of sugar. On January 26th her husband reported that the patient was much worse. She seemed delirious and would not take food. This condition had begun twenty-four hours previous to her husband's report. She was brought to the hospital in a comatose condition and was delirious at times. She was markedly jaundiced. Involuntary muscle twitchings were noted. The liver edge was not palpable and there was an increased area of cardiac dullness. Glucose and saline were forced intravenously and otherwise. Her temperature at the time of admission was 98.6°, pulse 110, blood pressure 120/75. Blood count: red cells 6,010,000, white cells 6,450, polymorphonuclears 74, small lymphocytes 24, monocytes 2. The blood urea was 27, cholesterol 176, total serum proteins 8.75, albumin 3.8, globulin 4.95.

At noon the following day the patient was catheterized and 200 c.c. of very dark colored urine obtained. She became restless and semicomatose. She was given glucose and saline intravenously, but her course continued to be progressively downward. The liver became quite atrophic as far as could be determined by percussion; there was almost no left lobe dullness, and the right lobe dullness appeared to be decreased by half. The urine which had to be obtained by catheter was scanty and contained bile 4+ and many bile stained casts. No tyrosin crystals were found in settled and centrifuged specimens. The patient died on January 30th. About thirty-six hours before death a great deal of pulmonary edema developed, but there was little or no general edema. The heart action was satisfactory at all times. The blood pressure fell gradually. Permission for an autopsy was refused.

Case 3.— The patient, a woman 31 years of age, was first seen at the Clinic on December 10, 1930. Two years previous to this time she had been operated upon for gastric ulcer, following which she had enjoyed good health until August, 1929. She then noticed a gagging sensation, with some soreness about the incision, and eructation of gas. The taking of food usually but not always aggravated the symptoms. Progressive fatigue developed, accompanied by pain in the joints, especially in the right shoulder, the right wrist, both knees and the sides of the neck. No swelling or

redness of these joints was noticed at any time, but a creaking was constantly present. The symptoms were worse during the mentrual periods. The gastric symptoms occurred about an hour after meals; there was no nausea or vomiting but appetite was decreasing and the patient was constipated.

The family history was unimportant. The patient had had no serious illnesses. Two operations had been performed — a uterine suspension in 1923 and a gastroenterostomy (ulcer) in 1928.

Physical examination revealed a well- nourished, well-developed woman 5 feet 7 inches in height, weighing 162 pounds. The temperature was 98°, pulse 72, blood pressure 132/88. The tonsils were large and appeared to be infected. Tenderness was present in the mid-epigastric region but no masses could be felt. The liver and spleen were not palpated. There were suprapubic and upper right rectus scars. On passive movement of the right wrist a creaking sensation was produced. Other joints appeared normal. The nose and throat examination disclosed hypertrophied and infected tonsils, chronic catarrhal maxillary sinusitis and ethmoiditis.

Upon dental examination, two devitalized teeth were found, and two others showed periapical absorption.

The tentative diagnosis at this time then included possible marginal ulcer, dental sepsis, infected tonsils, sinusitis, chronic ethmoiditis, mild chronic infectious arthritis.

An x-ray examination of the gastrointestinal tract showed the stomach and gall bladder to be functioning normally. A gastric analysis showed 23 per cent free acid, 36 per cent total acid. The patient was given an alkaline powder, and atropine sulphate gr. 1/100 b.i.d. and was advised to have her teeth extracted.

On December 22nd she was feeling better and was given a prescription for belladonna, hyoscyamus and bromide.

On January 7th she complained of stiffness in the neck, right shoulder, back and arms. She was again advised to have her teeth and tonsils removed and was given a prescription for cinchophen grs. 7.5 t.i.d.

On January 28th she reported that she had had her tonsils removed two weeks previous to that time. During the previous week she had been nauseated and on the day upon which she reported to the Clinic she had vomited some green fluid. On the previous day she had noted some itching of her hands and feet. She had had no cinchophen for a week, having had a total of 150 grains. On

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February 2nd she had been vomiting and suffering from gas and pain in the stomach. She was very sleepy. The urine was quite dark, the vomitus was yellow in color and slimy. The patient had had several red "blisters" under her skin. Two days previously she had noted that her eyes were getting yellow.

Examination showed her to be quite jaundiced and excoriations were noticed on the legs due to scratching. There was a small spot to the inner side of the left knee and one on the palm of the left hand. There were a few black and blue marks on the right leg, above the knee, not due to trauma. The liver was tender but not palpably enlarged. There was an area of infected granulation in the upper jaw at the site of an extracted tooth.

The impression was cinchophen toxemia and infected dental granulation. The patient was given alkaline powders, a high carbohydrate diet was advised, and she was instructed to take a drahm of phosphate of soda every morning.

On February 17th the jaundice had increased, and the stools were gray. The patient was admitted to the hospital for treatment.

On examination she was found to be dehydrated and deeply jaundiced; she presented a toxic appearance, but was not undernourished. The right lobe of the liver was palpable at the costal margin. The left lobe seemed definitely smaller to percussion. No tenderness was present. The spleen was not palpable. The temperature was 98.6°, pulse 83, blood pressure 105/75. The patient was vomiting and appeared to be quite ill. She improved rapidly upon administration of glucose intravenously and a high carbohydrate and low fat diet. On February 23rd the right lobe of the liver could not be palpated and both lobes appeared smaller to percussion than before. At present the patient is almost well and will be discharged from the hospital within the next few days.

SUMMARY

The above brief review of the history and pharmacology of cinchophen, the symptoms of toxemia resulting from the use of the drug and the method of treatment described prove definitely that the administration of this drug may be attended with grave danger, one of the three cases reported here having terminated fatally.

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THE NATURE OF LIVING CELLS

WITH SPECIAL REFERENCE TO THE NATURE OF CANCER CELLS AND
OF FATTY DEGENERATION

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AMY F. ROWLAND

The research a preliminary report of which is here presented was
undertaken with the purpose of discovering some physical principle
that might account for the conversion of normal cells into cancer
cells, that is, into cells the energy of which is used only for growth,
whereas the energy of the tissue in which the conversion takes place
is used primarily for function. It is clear that the cancer cell must
owe its formation to the operation of existing laws of growth in the
host. These laws are most strikingly illustrated in the process of
fertilization.

The ovum and the sperm, as Keller has shown, exhibit opposite
signs of charge, hence they attract each other. The preponderantly
positive element exists apart from the preponderantly negative
element, but when they unite growth and division take place, form-
ing the beginning of a new organism. The fertilized ovum contains,
therefore, elements bearing opposite signs of charge and electrolytes
in optimum proportions, and transmits these characteristics to each
cell of the developing organism.

Every living cell contains proteins, lipoids and electrolytes.
Colloidal systems of proteins and of lipoids bear different degrees
of electrical charge. We postulated, therefore, that if we were to
mix proteins and lipoids with the electrolytes present in living tis-
sues, the same laws would act that govern the process of fertiliza-
tion; that is, that the comparatively positive element would combine
with the comparatively negative element, this combination with the
electrolytes carrying an electric charge and forming an organized
unit which would present a cell-like form. In other words, we pro-
posed to test by experiment whether or not after the essential frac-
tions of the cells of an animal had been separated they could be
reassembled to form a lower undifferentiated type of cell that would
bear a certain physical resemblance to the cell from which the
material of which it was made was derived, and would also exhibit
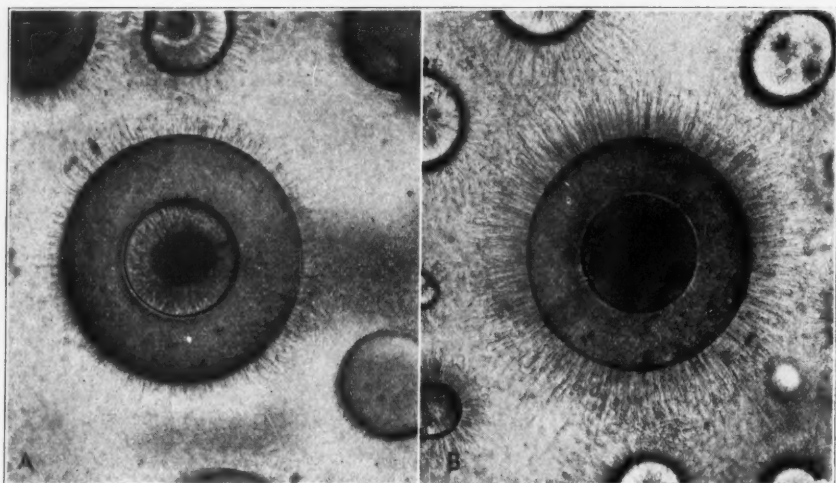some of the phenomena of the parent cells.

Fig. 1. Photomicrographs of the same ciliated autosynthetic cell taken fifteen miuntes apart: *A*, short and sparse cilia; *B*, long and abundant cilia.
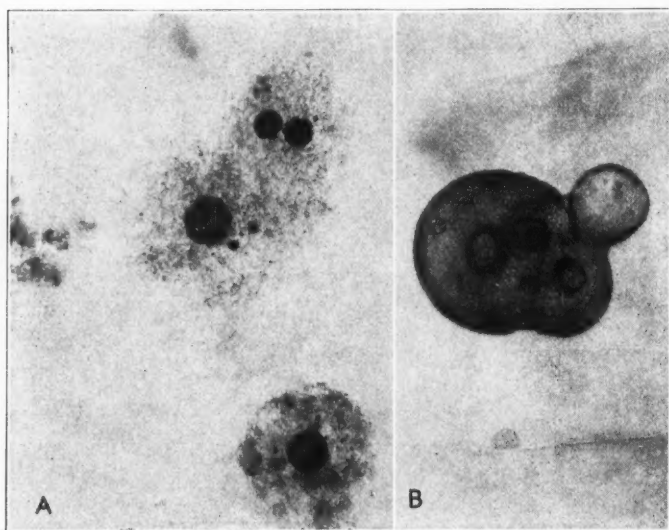

Fig. 2. Division of autosynthetic cells by fission (*A*) and by budding (*B*). The cells shown in *A* were stained with hematoxylin-eosin.

This research is by no means the first attempt to produce artificial cells. Such cells have been formed from inorganic and organic material by many investigators, notably Beutner, Butschli, Herrera, Le Duc, Lehmann, Loeb and MacDougal. The cells formed by these investigators have shown such phenomena as division, nucleation, growth and ameboid movement, but in cells made by their formulas, respiration, repeated division and prolonged exhibition of the manifested phenomena have not been observed. The cells of MacDougal showed a difference in ion concentration analogous to biologic cells. The investigations of Bastian and others are of a different type.

As we have stated, it has been our hope that from the study of undifferentiated cells made up of proteins, lipoids and electrolytes extracted from tissues, we might ultimately gain some insight into the processes whereby malignant cells are formed from the proteins, lipoids and electrolytes of their parent tissues.

To these cells thus formed from proteins, lipoids and electrolytes we have applied the term autosynthetic cells. We expected that, because of the potential differences between the elements from which they were synthesized, these autosynthetic cells would themselves carry an electric charge and would show growth energy; that they would divide, would have respiration and would show motility. The extent to which our expectations have been realized is stated in the following summary of experiments.

EXPERIMENTAL OBSERVATIONS

From the organs of freshly killed normal animals, the lipoids and proteins of the brain were extracted and the ash was obtained. By mixing the lipoids and the proteins of the brain and a solution of the brain ash or of the electrolytes contained in the brain, the process of fertilization in nature by the uniting of the spermatozoon and the ovum was imitated.

On observation of this mixture of lipoids and proteins of the brain and the solution of electrolytes under the microscope, we noted immediate activity of organization. Cell-like forms appeared and grew slowly (Fig. 1). They multiplied, sometimes by budding, and sometimes by direct divison (Fig. 2). These cells were nucleated; they took vital stains; they consumed oxygen; they gave off carbon dioxide. Under a high power lens, free movement of granules and a movement not unlike the brownian movement were seen, and sometimes the movement was so rapid that it was difficult to keep the cells in the field of vision of the microscope. Some of these mixtures have continued to show active cells for two and one-half months.
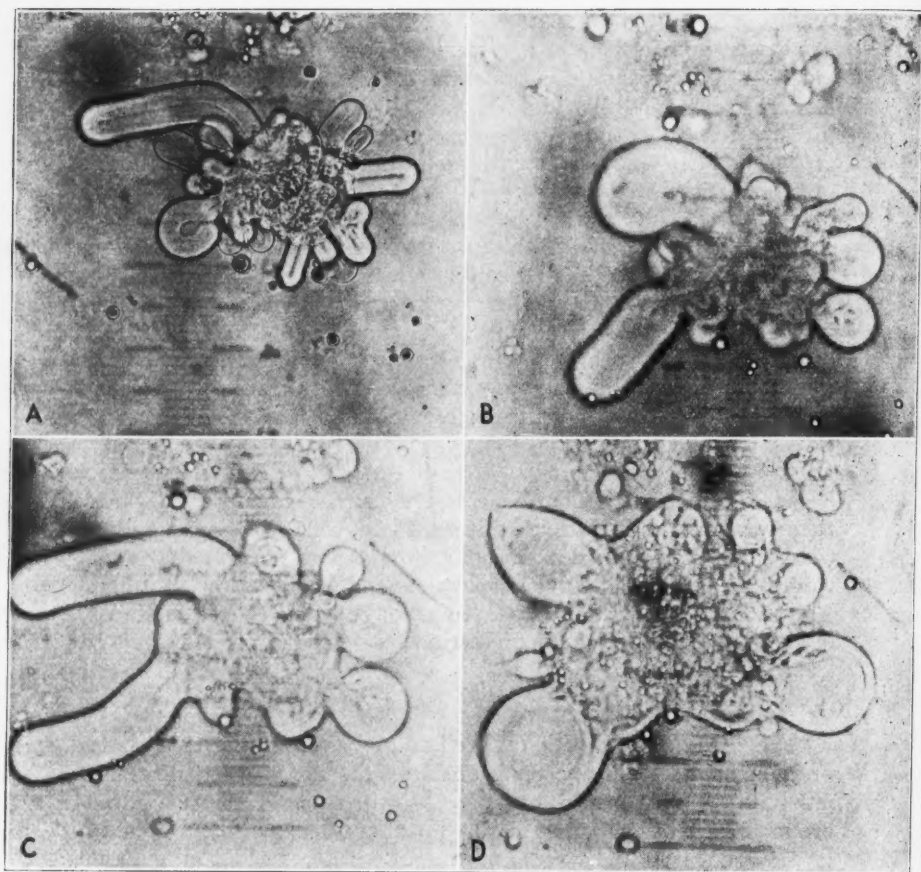
Fig. 3. Successive stages in the growth and movement of an ameboid auto-synthetic cell. Forty-eight photomicrographs of this cell were taken at intervals of fifteen minutes. The photomicrographs shown here were taken at the following intervals after *A: B*, one hour and forty-five minutes; *C*, four hours and forty-five minutes; *D*, eleven hours and thirty minutes.

Exactly the same technic was carried out for the other organs of animals. The lipoids and proteins of the various organs other than the brain were extracted and the ash was obtained; but on mixing the lipoids, proteins and a solution of the ash of these various organs, only feeble or no power of organization was seen. The nearest approach to organization in extracts from organs other than the
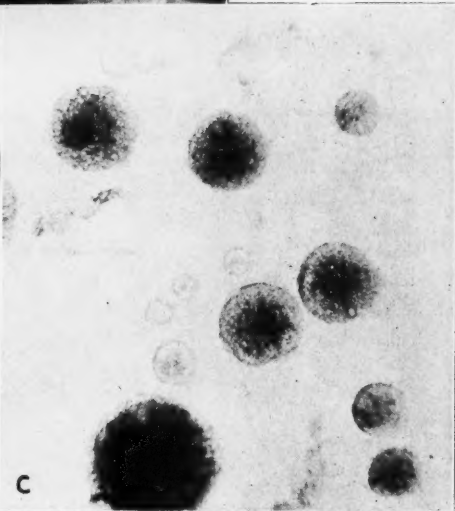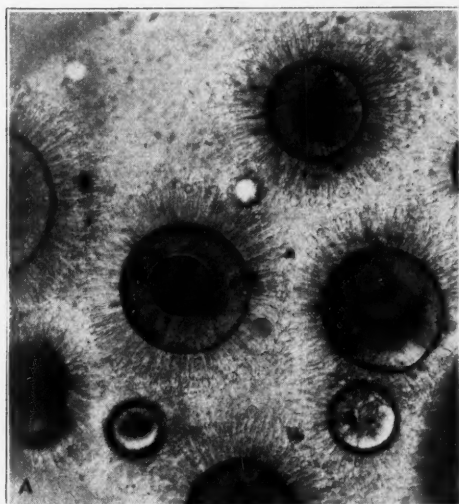
Fig. 4. The effect of exhaustion on the formation of autosynthetic cells: *A*, normal autosynthetic cells; *B* and *C*, unorganized masses produced in the mixture of protein and electrolyte solution with *B* the lipoid extracted from the brain of a rabbit that died of exhaustion from insomnia, and (*C*) the lipoid extracted from the brain of a dog that had died from distemper.
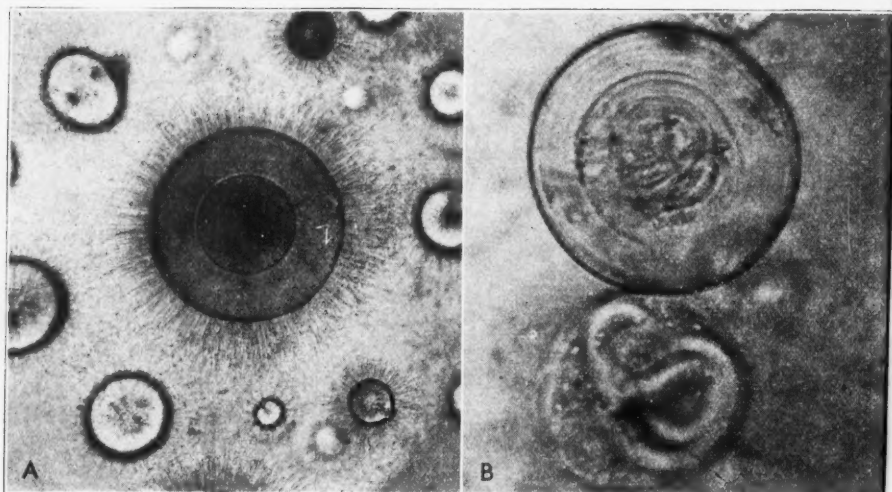
Fig. 5. The effect of radiation on autosynthetic cells: *A*, normal autosynthetic cell; *B*, radiated autosynthetic cells. Note the unorganized masses of fat within the cell membranes.
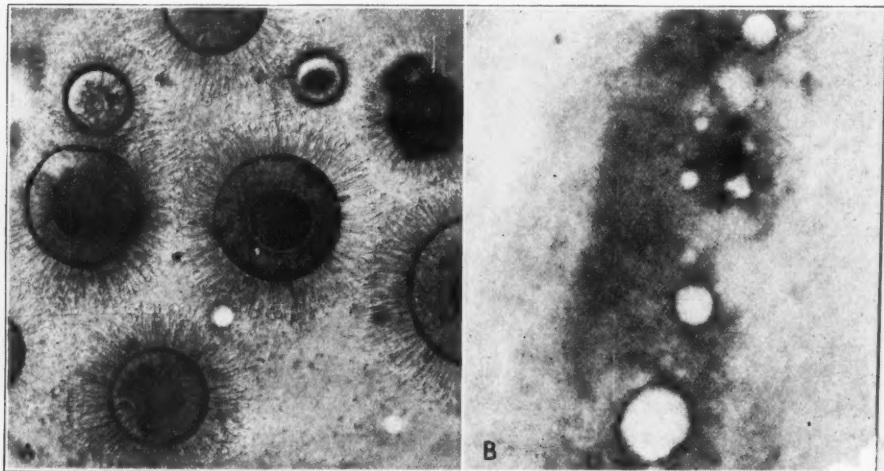
Fig. 6. The effect of lack of oxygen (asphyxiation) on the production of auto synthetic cells: *A*, normal autosynthetic cells; *B*, lack of organization and fatt droplets in a mixture of electrolyte solution and protein with lipoids which had been shut away from the air for a number of weeks.

brain was in the case of the spleen, and to a lesser degree of the ovary and the testes, but the organization seen in these cases was not at all of the same order as that which took place in the mixture of the elements of the brain.

We next observed the effects of adding the lipoids of the brain to the proteins and solutions of the ash of each of the other organs. Immediate organization was observed. The cell-like structures that were formed took vital stains; they grew in size; they multiplied and showed respiration. This experiment revealed clearly that the lipoid of the brain is unique in being the possessor of a structure that has the power of organizing the proteins of any organ.

As we have stated, these autosynthetic cells took vital stains (Fig. 2A). They grew and multiplied. They showed internal organization such as a nucleus, granules, etc. They varied considerably in size. They had respiration, their consumption of oxygen running as high as 14 mms. per hour per 2 cc. of cell mixture over a period of five hours, the respiratory quotient ranging from 0.7 to 0.98. Some of these cells were obtained for a period of nine hours, and many photographs showing the changes in their form were taken. The form of the cells seemed to depend on the pH of the electrolyte solution, ciliated cells being always produced in a solution of pH 7.5.

While carrying out the effects of adding various "food" substances to the cells, it was found that dextrose increased the metabolism of the cells while the various culture materials such as beef broth, agar, blood serum, etc. showed little or no effect. It is necessry, however, in order to keep cultures alive over a period of time, to feed them by the occasional addition of protein. In one case suprarenal protein was added, and the cell immediately assumed the appearance of an ameba and pseudopodia like those of an active ameba were thrust out. Occasionally the cell moved, apparently without first thrusting out pseudopodia, although the usual manner of movement was by thrusting out of a loop of fiber-like substance from the body of the organism, into which loop the contents of the organism, the granules, etc., seemed to flow, the organism moving in the direction of the flow (Fig. 3).

Of special significance was our observation that autosynthetic cells were not formed in the brain-lipoid-brain-protein, electrolyte mixture of dogs which had died from distemper. In rabbits that had died of exhaustion from insomnia, unorganized masses appeared in a mixture of this kind (Fig. 4).

On the addition to the brain lipoids and proteins of an electrolytic solution identical with the brain ash solution, with the exception that the potassium salt was omitted, the formation of cells was
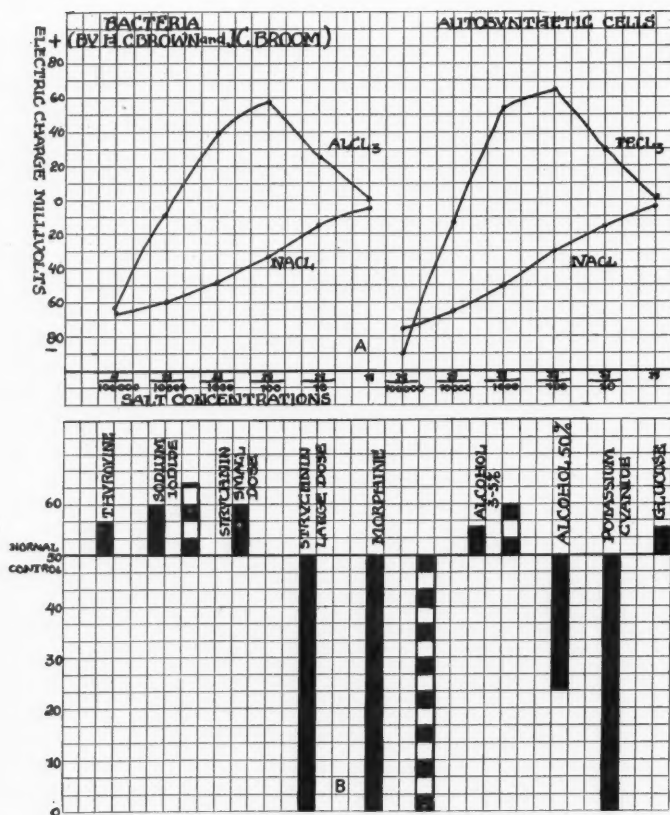
Fig. 7. The potential difference of autosynthetic cells. *A* shows the effects of varying concentrations of sodium chloride and ferric chloride on the potential difference. Compare the curve for the autosynthetic cells with that for bacteria as established by Brown and Broom. *B* shows the effects of various agents on the potential difference. (The potential difference of the cells was measured by cataphoresis; that of the ameba by a direct electromotive method.)

delayed, and the cells differed in form from those found in the complete brain ash solution. It should be noted that the lipoids themselves held adsorbed potassium ions. Could all the potassium be eliminated, it might be that the organization of cells would be entirely inhibited.

In collaboration with Dr. Otto Glasser of the Cleveland Clinic Radiation Research Laboratory, we subjected the lipoids of the brain to intense radiation before they were mixed with the proteins of the brain and the electrolyte solution, and we found that the mixture had lost the power of organization — no cells were formed. The radiated lipoid material assumed the aspects of a different substance. Small globules, apparently resembling neutral fat, appeared, suggesting that radium dislocates the metal elements, viz., the molecules of potassium and of phosphorus that bind together the delicately poised elements of the cell. Radiation of newly formed cells broke them down (Fig. 5). On the other hand, radiating the protein had no effect. Autosynthetic cells were formed with radiated protein and with nonradiated lipoid as freely as with nonradiated protein. It would seem that the lethal effect of radiation must be exerted on the lipoid element of cancer cells.

Cataphoretic measurements have been made from which the electric charge of the protein, of the lipoid and of the structures have been calculated. There was a marked potential difference between the lipoid and the protein, and the charge on the cells has been found to vary from 50 to 70 millivolts.

Direct measurements of the electric potential difference of the cells and of the nucleus and cytoplasm were made by introducing electrodes into them. The nucleus was found always to be positive with relation to the cytoplasm, the difference of potential varying between 20 and 30 millivolts.

When "old lipoids," that is, when lipoid material that had been kept over a number of weeks and had been shut away from the air was used, we observed that instead of organized autosynthetic cells, fatty droplets were formed (Fig. 6). These fatty droplets which were similar to those seen after the lipoid had been radiated were seen also after cyanide was added to the lipoid mixture and after the structures were deprived of oxygen, that is, asphyxiated. The phenomenon apparently corresponds to fatty degeneration.

The effects of the addition of various agents to the mixture of lipoid, protein and electrolyte were as follows: Both the potential difference and the respiration were decreased on the addition of an anesthetic (urethan) (Figs. 7 and 8). (*Note:* The effect of ether and of chloroform could not be tested as they immediately dissolved the

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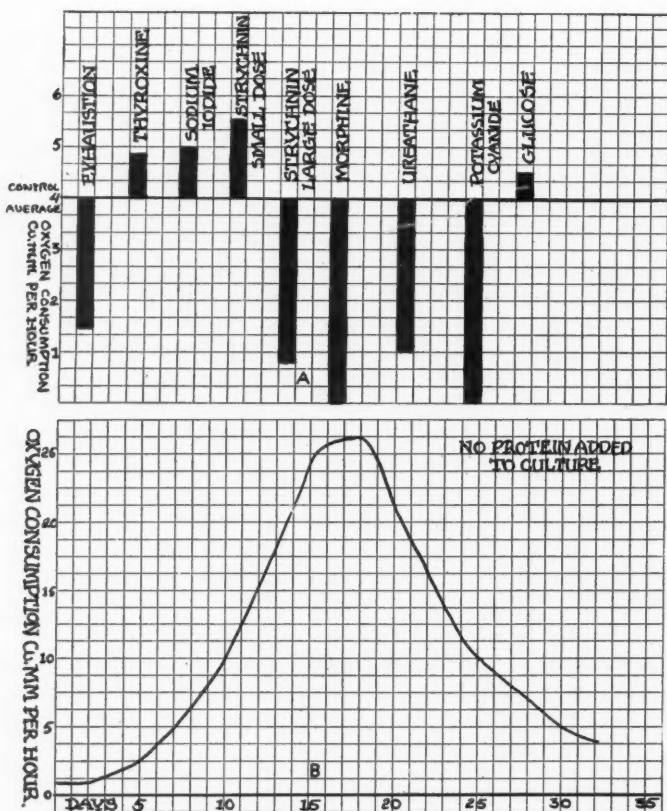
Fig. 8. The oxygen consumption of autosynthetic cells: *A*, The effect of various agents on the oxygen consumption of autosynthetic cells; *B*, The progressive changes in the oxygen consumption of autosynthetic cells during thirty-four days.

lipoid.) The addition of salts in various concentrations affected the potential difference of our autosynthetic cells in a manner strikingly similar to the effect of the same concentrations on the potential differences of bacteria (Brown and Broom) as is shown by the plotted
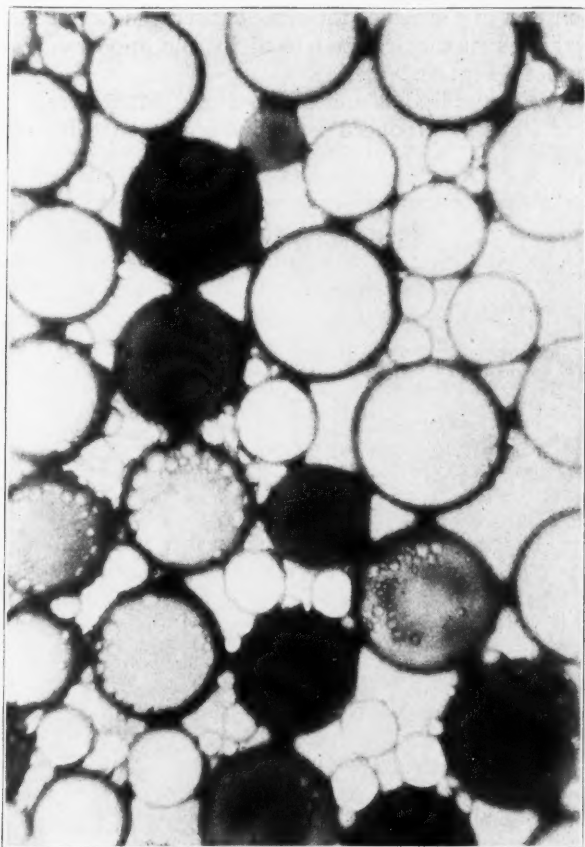
Fig. 9. Unorganized masses produced in a mixture of electrolyte solution with the lipoid and protein extracted from a cancer.

curves in the chart. Both the potential difference and the respiration of the autosynthetic cells were increased on the addition of some agents. The potential difference and the respiration were decreased on the addition of morphine. On the addition of a small amount of strychnine or of alcohol (from 3 to 5 per cent), the potential dif-

ference was increased. On the addition of large amounts of either strychnine or alcohol (50 per cent), the potential difference was decreased. On the addition of a cyanide or of a toxin, the potential difference was decreased to zero.

The lipoids and proteins extracted from a cancer, when mixed with a solution of the ash of the same cancer, did not produce cells, but a bizarre structure characterized by the appearance of many fatty droplets (Fig. 9).

A mixture of the lipoids and proteins of a human brain with the electrolyte solution produced a highly organized cell with active division (Fig. 10).

Fig. 10. Autosynthetic cells produced in a mixture of electrolyte solution with the lipoids and proteins extracted from a human brain. Note the active division in progress in (B).

SILENT LESIONS OF THE UPPER URINARY TRACT

William E. Lower

A certain percentage of lesions of the upper urinary tract do not produce any outstanding subjective symptoms which obviously pertain to the kidney and the ureter. Because of this fact we designate them "silent lesions," and because of the absence of symptoms referable to the urinary tract an incorrect diagnosis is often made with unfortunate and sometimes fatal results. It must not be understood that many of these lesions do not give any symptoms, but the symptoms are not referable to the organ diseased.

Prominent among these lesions are kidney tumors, kidney stones and often ureteral calculi as well, but hydronephrosis, inflammatory conditions, certain anomalies of the urinary tract and other conditions should also be included. Pyonephritis, pyelonephrosis, pyelitis, hydronephrosis, nephroptosis, and ureteral stricture also may fail to produce any characteristic symptoms referable to the seat of the lesion. The symptoms of any of these conditions may apparently relate to the gastro-intestinal tract, to the spine, to certain orthopedic conditions or in women, in particular, to the genital organs.

It is apparent, then, that the location of the discomfort as described by the patient is not always a dependable guide and that the answer to the question: "What is your complaint?" may be most misleading. Of course a physical examination will often readily disclose the real lesion, but too often a complete examination is not made or the attention of the physician may be directed entirely to the area of referred discomfort or pain and the treatment is directed accordingly.

It should be noted also that pathological conditions of the urinary tract may coexist with lesions elsewhere, and therefore microscopic as well as chemical examination of the urine should form a part of every routine examination, and in the presence of pus or of red blood cells a searching examination with the cystoscope and with the aid of the roentgen ray should be made to rule out or to establish the presence of a lesion within the urinary tract.

Not only may symptoms of the above-cited lesions be entirely referable to the gastro-intestinal tract, to the spine or to the genital organs, but the presence of what is called the reno-renal reflex may cause a mistaken diagnosis; that is, the symptoms of a lesion

of one kidney or ureter may be referred to the opposite kidney or ureter, but this is exceedingly rare.

Cases of renal calculus may present symptoms all of which point to an acute abdominal condition, and especially when these symptoms are referred to the right lower quadrant a misleading conclusion is apt to be drawn. In such cases, many an innocent appendix has undoubtedly been sacrificed while the guilty kidney or ureter has remained, with the continuance of the symptoms and perhaps ultimate disaster.

In many cases stones may remain quiescent for many years without causing any symptoms. A stone may even cause extensive destruction of the renal parenchyma while presenting either no symptoms or none more significant than a dull backache or chronic cystitis. Both kidneys may be filled with stones and the patient never have a renal colic. I have seen a number of such cases.

Nausea and vomiting, epigastric pressure, general and local abdominal pain, pyrosis, belching of gas and constipation are so frequently associated with kidney and ureteral lesions that it is not surprising that a lesion of the gastro-intestinal tract is often first suspected. Pain in the right lower abdominal quadrant is so often present that it is not strange that the appendix is often falsely accused, while backache and shooting pains direct suspicion to the neuromuscular system. The metabolism is so often disturbed that the endocrine system may come under suspicion; while frequently palpitation and anginal pain suggest an involvement of the cardio-vascular system.

In women the symptoms of pathological conditions in the urinary tract closely resemble those presented by lesions of the genital organs. Therefore, as we have already pointed out, an examination of the urine is essential for the establishment of the differential diagnosis. In such cases the presence of pus and of blood cells in the urine may easily be misinterpreted, so that only specimens secured by catheterization should be used.

Only in recent years has it been generally realized that most of the lesions of the urinary tract may occur in children as well as in adults. The refinement of diagnostic measures now makes it possible to examine children with little if any more difficulty than that required for the examination of adults. It should be borne in mind that in young children it is often difficult to elicit a description of subjective symptoms, so that one must place greater dependence upon objective findings than in the case of an adult. The significance of enuresis, in particular, should not be dismissed with the casual conclusion that it is of nervous origin or due to cystitis, and it

should be borne in mind that pyuria may be a sign of a surgical lesion of the upper urinary tract as well as of cystitis. Enuresis should lead to a suspicion of the presence of renal tuberculosis, as enuresis is a prominent symptom of this condition. It is a well known, but too often overlooked fact that a solid tumor in a child's abdomen is nearly always a renal tumor. A congenital polycystic kidney is nearly always painless and may grow to a great size without causing any discomfort. As these tumors are nearly always bilateral, the diagnosis is easily made.

It is not necessary to enumerate here the symptoms of those lesions which relate directly to the kidney and ureter, as when such symptoms are present no difficulty in diagnosis is presented. I wish merely to emphasize the importance of the urological examination in any case of generalized or localized symptoms the cause of which is not obvious, and to urge the microscopic examination of the urine as a part of every routine examination, with immediate reference of the patient to the urologist if pus or red blood cells are found.

Our attention has so often been called to the existence of these silent lesions of the upper urinary tract by their discovery in the course of routine x-ray examinations for gastrointestinal complaints or of orthopedic examination for backache, sacro-iliac discomfort, etc., that I decided to make a study of a group of lesions of the upper genito-urinary tract to determine how frequently they had existed without causing any subjective discomfort directly at the seat of the disease.

In a series of 637 cases of kidney lesions on which there were sufficient data it was found that in 33.1 per cent no symptoms referable to the kidney were present, the patients complaining rather of discomfort in other parts of the body. In 15.3 per cent of the cases the symptoms were entirely referable to the bladder; in 9.5 per cent, to the gastrointestinal tract or back, hips, chest, etc., while in 8.3 per cent the lesion was entirely symptomless so far as the subjective discomfort of the patient was concerned, having been detected in the course of the routine examination from the presence of blood or pus in the urine.

Among cases of tuberculosis of the kidney, symptoms were referable to the kidney in only 27.5 per cent of the series, so that in 72.5 per cent no symptoms referable to the kidney were presented. In this group, in 62.3 per cent the symptoms were referable to the bladder and many of these cases were therefore treated for the cystitis which was secondary to the tuberculous lesion in the kidney. I believe that if the frequency with which this error is made were

generally known, these cases would not be subjected for so long a period to the treatment of the secondary lesions.

Among cases of tumor of the kidney, in 50 per cent the symptoms were not referable to the kidneys and attention was directed to the kidneys only because of the presence of blood in the urine, or in children because of an abdominal tumor. Since stones in the kidney and ureter are of such common occurrence, it is fortunate that the proportion of cases in which the symptoms are not referable to the kidney and ureter is much less than in the types of cases cited above, yet in 19.3 per cent of the cases in our series the discomfort was referred to other areas than that of the upper urinary tract. Many of these cases presented gastro-intestinal symptoms — an observation which accounts for the large number of mistaken diagnoses and often unnecessary abdominal operations.

Among the cases of hydronephrosis in this series, in 38.4 per cent no symptoms referrable to the kidney were presented. The "silence" of these cases is readily understood, since often hydrone-phrosis is due to a congenital stricture at the uretero-pelvic or uretero-vesical junction, or to aberrant blood vessels which obstruct the ureter, the dilatation being so gradual that a marked crisis may never occur.

Among the cases of pyelonephrosis in this series, 62.4 per cent did not present any symptoms referable to the kidney; 16.6 per cent of this group were symptomless, and in 37.5 per cent the symptoms were referable to the bladder only. Among the cases of perinephritic abscess, 60 per cent presented symptoms referable to the kidney, the remainder being symptomless or presenting symptoms not referable to the upper urinary tract. Of particular interest were the cases of hematuria, among which 71.3 per cent did not present any symptoms referable to the upper urinary tract. Generally hematuria presents a peculiarly interesting and important problem, since if the lesion is in the kidney it may not be recognized until a blood clot or some tumor tissue obstructs the ureter and produces the charac-teristic renal colic. To await such an event before a diagnosis of the source of the hematuria is made may mean that the condition will then have progressed too far for satisfactory treatment to be applied.

In passing I might suggest that chronic prostatitis, now so fre-quently observed, seldom presents symptoms referable to the prostrate gland, but in any case of arthritis in men, the prostrate should be checked.

The following case histories are offered to illustrate the diagnos-tic difficulties which are presented by some of these cases of silent lesions of the upper urinary tract:

Case I

The patient was a woman, 39 years of age, who came to the clinic complaining of pain in the side, and nervousness. Six years before, after a miscarriage, an infection had occurred and severe peritonitis had developed. For the past five years she had had periodic attacks of pain which occurred quite regularly before the menstrual period, were very severe, lasted for several hours, and were located over the right iliac crest. She had an uncomfortable feeling in the right groin most of the time, this feeling being relieved by heat and rest and sometimes by codein. She was sometimes nauseated during the attacks of pain, but she never vomited. She could always eat and the pain was not related to diarrhea or constipation. She was never jaundiced. During the duration of the pain there was urgency and frequency, but no pain or blood or burning accompanied micturition. She had no palpitation, cough or edema, no headaches or dizziness. For years she had taken bromids for insomnia. For the preceding two months she had had stiffness of both hips and moved with considerable pain.

Examination of the urine showed nothing of importance, but on x-ray examination the roentgenograms of the gall bladder showed six stones clustered in the region of the gall bladder. A pyelogram of the kidney, however, showed a localized hydronephrosis in one of the upper calices and it was concluded that this contained the calculi.

At operation six renal calculi were removed from the right kidney.

Comment: In this case the patient had suffered for five years under the misapprehension that her pain was due to a menstrual disturbance.

Case II

The patient was a man, 46 years of age, who came to the clinic complaining of frequency of urination. Six years before he had had an attack of influenza and about the same time he had hematuria which he characterized as "complete," that is, not terminal. Three days later he had a milder hemorrhage. There was no obstruction to urination. The doctor who examined him first said that he had inflammation of the bladder and later that his trouble was prostatitis. Recently his only symptom had been frequency of urination with occasional shreds in the urine. Three weeks before our examination he had had some sharp pains in the right side.

The first clinical impression was that he was suffering from chronic prostatitis and chronic cystitis.

Microscopical examination of the urine showed a few red blood cells and 25 to 35 pus cells per high power field. The roentgenograms showed no suspicious shadow in the gastro-intestinal tract; a pyelogram, however, showed an enlarged pelvis on the left side and on the right a catheter passing for only a short distance into the ureter. Cystoscopic examination together with examination of the catheterized specimens led to a suspicion of renal tuberculosis on the right side with stricture of the right ureter.

At operation a rather small right kidney was removed, sections through which showed fairly numerous, rather large tubercle formations, enough of which were present to warrant an unquestionable diagnosis of tuberculosis of the kidney.

Comment: For six years this man had been treated for cystitis and prostatitis, the true condition being diagnosed only by pyelographic and cystoscopic examinations.

Case III

The patient was a man, 26 years of age, who came to the clinic complaining of sharp pain in the left side which he had experienced for the preceding eight months. The pain was accompanied by nausea and epigastric pain. He presented no symptoms referable to either the kidney or the bladder. Palpation disclosed tenderness over the lower left abdomen and inguinal region.

X-ray examination disclosed the presence of a small shadow in the region of the right kidney that might be due to stone.

Cystoscopic examination verified the diagnosis of calculus.

Comment: In this case there was nothing in the history or clinical symptoms to suggest the presence of a calculus in the kidney .

Case IV

The patient was a married woman, 49 years of age, who came to the clinic complaining of numbness of the feet and fingers, which had been coming on during the preceding six months. The neurological examination suggested peripheral neuritis. Examination of the urine, however, disclosed an occasional red blood cell and numerous pus cells — 75 to 100 per high power field. Cystoscopic and roentgenographic examinations were made, the latter of which revealed the presence of a large ¦calculus in the upper left ureter or kidney pelvis. The former revealed an infected calculus in the left ureter with an infected left hydronephrosis.

Nephrectomy was advised, but the patient has not as yet consented to have the operation performed.

Comment: This is a case of special interest in view of the neurological symptoms for which no other cause than the condition of

the kidney could be found on examination. This would have been missed had it not been for the urinary findings.

CASE V

The patient was a married woman, 23 years of age, who came to the clinic complaining of persistent pain in the right upper abdominal quadrant which had been present for two years. A diagnosis of cholecystitis with stones had been made, and three weeks before she came to the clinic a cholecystotomy had been performed at which no stones or other pathological condition of the gall bladder had been found. The symptoms had been unrelieved.

A roentgenogram taken after the injection of sodium iodid showed dilatation of the right ureter above a stricture, and the diagnosis of hydronephrosis was made. Dilatation of the ureter relieved the symptoms.

Comment: In this case, an examination of the urinary tract would have saved the patient a useless and serious operation.

CONCLUSION

In conclusion, may I impress upon you the fact that if you wait for the organism to indicate plainly the particular organ involved, especially in the case of the upper urinary tract, you will miss many diagnoses and many cures which might have resulted had you made an early diagnosis.

SILENT LESIONS OF THE KIDNEY

(Figures represent percentage of total number in each series of cases)

	Total Proven Cases	Tuberculosis	Tumors	Stones	Hydronephrosis	Pyelonephrosis	Multiple Infarcts	Ptosis	Anomalies	Perinephritic Abscess	Hematuria
With symptoms referred to kidney	66.8	27.5	50.0	80.6	61.5	37.5	100.0	42.9	----	60.0	28.5
Without symptoms referred to kidneys	33.1	72.4	50.0	19.3	38.5	62.4	----	57.0	99.9	40.0	71.3
Symptomless	8.3	5.8	27.8	3.7	7.7	16.6	----	14.2	33.3	----	38.7
With symptoms not referred to genito-urinary tract	9.5	4.3	11.1	9.7	7.7	8.3	----	28.6	----	20.0	12.2
With symptoms referred to bladder only	15.3	62.3	11.1	5.9	23.1	37.5	----	14.2	66.6	20.0	20.4

TYPES AND TREATMENT OF CHRONIC RHEUMATISM

Russell L. Haden

Definition

The use of the term "rheumatism" by clinicians has caused a great deal of confusion among physicians. It is not synonymous with arthritis, which includes all the inflammations of the joint, or with arthropathy, which comprises all joint diseases. It does not include gout, which is a disorder of metabolism accompanied by joint symptoms which are usually acute but may become chronic, nor does it include the chronic joint disturbances occurring in hemophilia and certain diseases of the nervous system. Likewise, those disorders are excluded which are the result of the localization in the joints of certain bacteria such as the tubercle bacillus, the gonococcus, the staphylococcus and other bacteria of specific type. In the latter group the lesion is a septic process best designated as specific infective arthritis, which is usually primarily an acute infection but may become chronic. The joint lesions are metastatic expressions of a blood-borne infection and the joints, at least during the acute stage, harbor the specific bacteria which incite typically a purulent effusion. It is evident also that joint disorders resulting from trauma alone, in which the lesion is local, should not be called rheumatism.

If one excludes gout, the arthropathies secondary to lesions of the central nervous system and similar disturbances, specific infective arthritis, and traumatic arthritis, there remains a great group of chronic joint diseases which are designated "chronic rheumatism." This is a constitutional or generalized disease accompanied by joint manifestations. The word "constitutional" should be stressed. It is defined by Webster as "belonging to, or inherent in the constitution or structure of body or mind."

Economic Significance

Few physicians realize the economic significance of chronic joint disease. Rheumatic diseases come third in the list of diseases for which physicians were consulted by the 15,000,000 insured industrial workers in Great Britain in 1927. Only bronchitis and diseases of the digestive system occurred with greater frequency. In the same year the British Ministry of Health paid out $25,000,000.00 in benefits

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for disability due to rheumatic diseases, representing a disability period of nearly 6,000,000 weeks.

In Sweden chronic rheumatism causes permanent invalidity in 9.1 per cent of cases. Every year 1,500 people are granted permanent invalidity payment as a result of rheumatism. In Austria upwards of two million Austrian shillings were paid to rheumatic patients in 1925 because of invalidity. In Switzerland, in 1927, 11.4 per cent of the total disability benefit which was granted was paid to rheumatic patients, and roughly, twice as many cases of permanent invalidity were due to rheumatism as were due to tuberculosis. The number of rheumatic patients in Hungary is estimated at 200,000 a year. Of the 7,297 permanent invalids in Denmark in 1923, 1,700 were suffering from chronic rheumatism. In Norway the number of invalids from rheumatism is estimated at one in 300 of a total population of 2,700,000.

Exact figures regarding the economic significance of rheumatism in the United States are not available in all cases. Pemberton[1] states that chronic arthritis was occurring at the rate of 60,000 cases yearly in the United States army at the time of the armistice. About one of every fourteen patients at the Mayo clinic in 1928 had one of the rheumatic diseases which constituted a primary or secondary diagnosis.[2] From recent surveys the Massachusetts State Department of Health estimates that there are at the present time in the State of Massachusetts, which has a total population of 4,380,000, 10,000 cases of cancer, 25,000 cases of tuberculosis, 85,000 cases of heart disease, and 150,000 cases of rheumatism. Every physician knows numerous patients who are unable to be productive members of society or are an economic burden on account of rheumatic disabilities. The full capacity for work of many others is seriously interfered with.

There has been little organized interest in rheumatism in the United States. Clinics for study and treatment of the disease have been organized here and there, but relatively little general interest has been shown by physicians. No problem in medicine is more difficult to handle or taxes more the ingenuity of the clinician; no disease touches on more fields in medicine or requires more careful team work in determining the cause and treatment. Two years ago an American committee, under the chairmanship of Dr. Ralph Pemberton, of Philadelphia, was selected to cooperate in an international movement for the study of rheumatism. This committee has held a number of meetings with the purpose of making plans to interest groups and individuals in the study of rheumatism, in promoting the organization of clinics and other facilities for the treat-

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ment of the disease, and for the stimulation of general interest among the laity as well as the medical profession.

CLASSIFICATION OF TYPES OF CHRONIC RHEUMATISM

Much of the confusion concerning rheumatism is due to the multiplicity of terms used in describing the disease and to the widely varying classifications of types. Osgood[3] has well reviewed the question of nomenclature and pointed out the important landmarks in the attempts at classification. An etiological classification is always the most desirable one, but this is impossible in the case of rheumatism because of the multiplicity of factors in etiology and the frequent doubt as to inciting causes of the disease. There is also no satisfactory clinical grouping. The best classification which is now available is based on the two fundamental pathologic changes occurring in the joint and investing tissues, and this classification coincides fairly well with clinical experience.

Nichols and Richardson[4] reported in 1909 the results of a careful pathologic study of fresh specimens of the joint tissues removed at operation and at autopsy in cases of chronic deforming arthritis. They recognized two great types. The earliest tissue change in one of these types is a proliferation of the synovial membrane and small round cell infiltration, with no marked changes in the articular cartilage or underlying bone. With the progression of the disease there is erosion of the articular cartilage as the granulation tissue extends over the joint surface, and finally there is bony ankylosis. Atrophy of the trabeculae is a striking feature. Nichols and Richardson spoke of this type of rheumatism as "*proliferative*."

The second type is characterized by a primary fibrillation or splitting of the joint cartilage and a later development of cartilagenous and bony overgrowths with little evidence of inflammatory changes in the cartilage or synovial membrane. The end result in this type is a loss of articular surfaces. Corresponding to the areas of eroded cartilage and bone, there takes place on the exposed articular surface a compensatory overgrowth of cartilage or bone which tends to keep the joint surfaces in contact. True bony ankylosis never occurs. Nichols and Richardson recognized a degenerative process as the fundamental factor and spoke of this type of rheumatism as "*degenerative*." They concluded that "these two types do not correspond to two definite diseases, but each represents reaction of the joint tissues to a considerable variety of causes."

Even before the existence of two primary pathologic types had been demonstrated, Goldthwaite had recognized two clinical types corresponding to the later work of Nichols and Richardson. The proliferative type he designated as *atrophic* since the constant and

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usually early characteristic as demonstrated by the roentgenogram is an atrophy of bone structure with later atrophy of articular cartilage. The second type, designated "degenerative" by Nichols and Richardson, was called *hypertrophic arthritis* by Goldthwaite since hypertrophy of bone seemed to be the only outstanding characteristic of the disease. Roentgenograms revealed little calcified spicules at the junction of articular cartilage and bone. In England the terms "atrophic arthritis" and "osteo-arthritis," which were introduced by Garrod in 1890, are used to designate these two types.

For the purpose of the present discussion all cases of chronic rheumatism may be classified as of the two types just mentioned — atrophic and hypertrophic. Other types of chronic joint disease such as gout or specific infective arthritis can be similarly classified pathologically. The specific infections cause a proliferative lesion, or the clinical atrophic type; the lesions secondary to central nervous system disease and gout result in a degenerative or a hypertrophic type.

The various classifications may be summarized as follows:

Author	Classification Based On	Types
Garrod (England)	Clinical data	(1) Rheumatoid arthritis (2) Osteo-arthritis
Goldthwaite (America)	Clinical and roentgenologic data	(1) Atrophic and (2) hypertrophic
Nichols and Richardson (America)	Pathologic data	(1) Proliferative and (2) degenerative

FUNDAMENTAL FACTORS IN THE ETIOLOGY OF CHRONIC RHEUMATISM

Chronic rheumatism is primarily a generalized or systemic disease. It is markedly influenced by factors which affect the body as a whole. There is always polyarticular involvement even though only one joint may show symptoms. Usually there is involvement also of other tissues, such as the muscles, tendons and nerves. The immediate cause of symptoms is a disturbance in the physiology of the joint.

Often there is a variation from the normal in the local metabolism which affects joint tissue as well as the tissue in other parts of the body. In the hypertrophic type of rheumatism the basal metabolic rate is usually below normal; in the atrophic type it may be either increased or decreased. Metabolic studies[5] show also an increased loss of calcium in the atrophic type and a retention of calcium in the hypertrophic type. Most important of all, there is marked im-

pairment of capillary circulation with a consequent denial of normal contact of the blood with muscle and joint tissue. Pemberton[6] has shown that this circulatory disturbance is responsible for a delayed removal of glucose from the blood stream. This is shown best by glucose tolerance tests. The disturbance in circulation in the extremities in the atrophic type is easily demonstrated in the peripheral capillaries of the finger. The surface temperature in this type of case is also below normal and the individual does not react normally to change in temperature.[7] Pemberton has been able to produce typical hypertrophic changes in the patella of a dog by impairing the circulation. Thus it seems quite possible that in both type circulatory changes may be the basis of the joint disturbance, although the mechanism of the change in the two types may be quite different. In the atrophic type all the tissues of the body are involved in addition to joint involvement; in the hypertrophic type the disturbances in circulation may be a localized expression of a generalized disturbance.

There is no one cause for chronic rheumatism. Perhaps most cases result from the interplay of several factors. The soil is often prepared for the disease or the symptoms are precipitated by exposure to cold or wet, fatigue of body or mind, or ill health from other causes. Certain possible factors in the two major types of chronic rheumatism may be discussed more fully.

Atrophic Type

1. *Infection:* This is a most important factor in the causation of the atrophic type. Every clinician sees patients who show a marked improvement or complete recovery following the removal of infection in teeth, tonsils, sinuses, prostate, or cervix. Other foci of infection such as the gall bladder occasionally give rise to the disease. Many patients show no improvement after an apparently complete eradication of foci of infection. In some cases this is probably due to remaining infection, but often the absence of clinical improvement shows that factors other than infection have produced the disease. There certainly is not conclusive evidence to show that one specific organism is the etiologic factor, even in cases which are definitely of bacterial origin.

Every patient with atrophic rheumatism should, however, have all foci of infection removed, but this should be considered the beginning and not the end of the treatment. Even if infection does initiate an arthritis it may have nothing to do with the carrying on of the pathologic process.

2. *Heredity:* The factor of faulty heredity is at times apparent. Heredity may influence the chemical constitution of the body, or

what is even more important, the physical make-up. Heredity can, however, only determine whether the individual is susceptible to the disease .

3. *Faulty Alimentation:* This term is used by Osgood to include the various disturbances and dysfunctions of the intestinal tract in rheumatism. The frequent incidence of anacidity or low hydrochloric acid in the gastric contents, the changes in the colon as demonstrated roentgenographically by Fletcher,[8] and the beneficial effects obtained by the administration of an adequate vitamin and low carbohydrate diet, all emphasize the importance of giving serious consideration to the intestinal tract in the treatment of the disease.

HYPERTROPHIC TYPE

1. *Disturbance of Metabolism:* Hypertrophic rheumatism is often associated with other conditions which we consider due to faulty body chemistry such as obesity, arteriosclerosis and essential hypertension. It frequently occurs at the menopause. There is much evidence to suggest that the symptoms of this form of rheumatism represent an accentuation of the normal ageing process. The joint tissues do not have the normal resistance to wear and tear at this time.

2. *Trauma:* Trauma must be a most important factor since the weight-bearing joints are the ones primarily involved. Any undue strain will hasten the fibrillation of cartilage and the forming of later lesions. Trauma alone should, however, not cause this change unless the normal resistance of the cartilage to erosion is lowered.

3. *Infection:* Infection probably plays no primary part in hypertrophic rheumatism from the standpoint of localization of bacteria in the joints, although bacteria may occasionally localize in a joint which is already damaged. At times an infection such as pneumonia acts as an etiologic factor by initiating a disturbance in metabolism with consequent alteration in body chemistry.

Precipitative factors are much less important in the hypertrophic than in the atrophic form.

SYMPTOMATOLOGY

The symptoms and clinical picture of rheumatism are too well known to every clinician to need description. The atrophic type occurs from infancy to middle age, women being more susceptible than men. It occurs almost always in the thin, asthenic, ptotic type of indiviual. The onset of the disease may be acute or insidious. The patient usually tires easily and is often anemic; the circulation is usually poor, as evidenced by cold and clammy hands and the

absence of superficial veins. The joints are swollen and contain an excess of fluid and pain is usually severe. As the disease progresses, stiffness, deformity often with bony ankylosis, and marked muscle atrophy occur.

Early in the course of the disease there is a loss of lime salts in the bone as shown by roentgenographic examination. Later there is definite bone atrophy, narrowed articular space, subluxation, and ankylosis.

The hypertrophic type of case presents a very different picture. The patient is usually past middle age, is robust and well nourished. The history of the disease is one of slow onset and slow progress and there are few symptoms referable to the disease except the joint disability. There is very little swelling of the joints and the pain and disability are slight. Muscle atrophy does not occur. The roentgenogram shows the characteristic lipping or marginal hypertrophy of the bone, which is best shown clinically by the presence of Heberden's nodes. Bony ankylosis never occurs, although there may be a fixation of joints due to contact of the hypertrophied bone with opposing joint surfaces. The fatigue and anemia which are present in the atrophic type of case are absent in the hypertrophic type.

COMPARISON OF ATROPHIC AND HYPERTROPHIC TYPES OF CHRONIC RHEUMATISM (PEMBERTON)

Atrophic Type	*Hypertrophic Type*
Age of onset usually below age of 40.	Age of onset usually after age of 40.
Patients often of asthenic build.	Patients often of robust build.
Onset usually slow but may be sudden.	Onset always slow.
Usually multiple involvement.	Often symptomatically a single joint is involved.
Systemic reaction may be profound.	Slight systemic reaction.
Large effusions common.	Slight effusion uncommon.
Appearance of joints tends to atrophy.	Appearance of joints tends to hypertrophy.
Ankylosis may supervene.	Bony ankylosis does not occur.

TREATMENT

The points already discussed should emphasize the necessity for a thorough survey of the patient before treatment is attempted. All factors which may possibly enter into the production of the disease must be evaluated and corrected. Patients with rheumatism have suffered often from a too narrow point of view as to etiology and treatment. One patient has teeth extracted, another has his

tonsils removed, the colon of another is irrigated. Perhaps he needed none of these; perhaps he required all three, or even more. No disease in medicine requires a broader point of view in regard to treatment — there is no single panacea.

Atrophic Type: All obvious foci of infection should be removed. The removal of infection should be only the beginning, not the end of the treatment. Faulty alimentation should be corrected by the use of dilute hydrochloric acid in cases of anacidity, a high vitamin and low carbohydrate diet, by laxatives and occasionally by irrigations of the colon. Physiotherapy is advisable for its local effect on the joint and for the general effect on the circulation. Active motion of the joint is desirable. Transfusion is often of the greatest aid as are also certain drugs such as arsenic and iodine. The institution of non-specific protein therapy or autogenous vaccine therapy is valuable.

Special exercises should be given to increase the vital capacity of the patient, to improve the intrathoracic and the intra-abdominal circulation, and to relieve the ptosis.

After the disease process has been arrested, orthopedic surgery may do much to relieve the deformities and limitation of motion.

Hypertrophic Type: Stimulation of metabolism and removal of the metabolic overload is the primary indication in treatment. Reduction in weight is indicated if the patient is over normal weight, therefore the diet should be low in carbohydrate and high in vitamin. Physiotherapy should be employed in the same way as in the case of the atrophic type. Certain drugs are useful, especially thyroid extract and iodine derivatives. Laxatives are often indicated. Rest and protection of the joints is very necessary and orthopedic measures designed to prevent any unnecessary strain should be employed.

Conclusions

1. Chronic rheumatism is best defined as a constitutional or generalized disease accompanied by joint manifestations.

2. From an economic standpoint, chronic rheumatism is of the greatest significance on account of its frequency and the disability, and in many cases permanent invalidity resulting from the disease.

3. From the clinical as well as the pathological point of view, the disease may be classified as of two types — atrophic rheumatism and hypertrophic rheumatism.

4. The fundamental factor in both types is probably a disturbance in the capillary circulation.

5. Various etiologic factors lead to the circulatory disturbance.

6. The treatment of chronic rheumatism should not be limited to any one method, but should include every aid possible which may bring about the recovery of the patient.

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THE LOCATION OF METASTASES FROM THE URINARY TRACT, THE PROSTATE, AND THE THYROID GLAND

B. H. Nichols

Before determining the type of treatment of definitely malignant conditions of the thyroid gland, the urinary tract, and the prostate, it is very important to determine the presence or absence of metastases from these malignancies. The finding of metastatic lesions by roentgenographic examination may confirm the presence of a primary malignancy in one of these organs.

In order to ascertain what organ harbors the primary lesion, it is necessary to know some of the characteristics of the areas of metastasis. Metastasis may take place by the lymphatic route. This is particularly true in the case of carcinoma, except of the adenocarcinoma type.

Metastases by the lymphatic route, however, can not well be determined by roentgenographic examination because enlarged metastatic lymph nodes can seldom be recognized by this method. We have chosen for discussion, therefore, those tumors which are more frequently disseminated by way of the blood stream on account of the more or less encapsulated character of the masses. In their metastatic growth these tumors appear as rather distinct, nodular, or well-defined masses which are quite similar in appearance. They are easily recognized in the chest as dense tumor masses (Figs. 1, 2, 3, 4, 5 and 6) and in the osseous system as rounded areas of destruction in the bones without any evidence of bone production (Figs. 7 and 8). (Fig. 11). The area in which these tumors grow, completely destroying the bone, is sometimes designated by the roentgenologist as a "punched out area." These punched out areas are characteristic of metastases from adenoma of the thyroid and from the hypernephroid tumors of the kidney and the metastatic lesions may have all the characteristics of the primary growth, while metastases from the prostate are of a different type, which will be described later.

The metastasis of benign tumors was first described by Cohnheim. He used adenoma of the thyroid as an illustration and expressed the opinion that the thyroid gland gives off adenomatous alveoli, which in turn are transplanted to other organs. There is no definite evidence that this takes place, and we believe that if these transplanted growths are found, they must be masses of aberrant thyroid tissue and not true metastases. We believe that all metas-
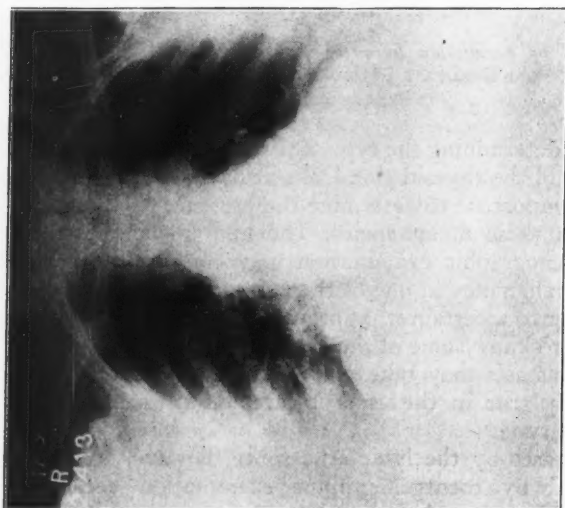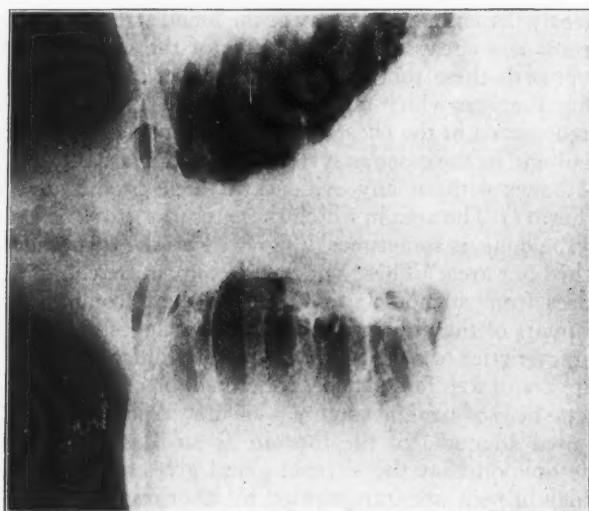
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Fig. 2

Fig. 1

tases from the thyroid are malignant, and therefore the finding of metastases, particularly in the chest, aids greatly in establishing the diagnosis of a suspected carcinoma of the thyroid.

In the case of malignant condition in the kidney, the character of the metastatic lesion may direct attention to the kidney as the primary focus when such a malignancy has not been previously suspected, and in many cases the finding of the metastases will confirm the suspicion of the presence of a kidney tumor, and may also show definitely that the growth is malignant. This is an interesting example of chest and skeletal metastases through the blood stream which closely simulates thyroid metastases.

In many cases of malignant hypernephroid tumors of the kidney, there is no hematuria or other urinary symptoms that would lead to the suspicion of a malignant condition in the kidney, a so-called silent kidney lesion. Likewise, many small hypernephromata may metastasize before a palpable tumor of the kidney can be recognized, and in such a case pylography is the only means of confirming the presence of the suspected lesion. These metastatic lesions, particularly skeletal metastases, were formerly thought to be adrenal rests, while in reality they are usually carcinomatous renal metastases. A bone tumor of this type may be only a single growth, the removal of which in some cases has resulted in no return of metastases. A single lesion of this kind in bone probably should be removed together with the primary growth.

Tumors of the prostate may be easily found by palpation. However, simple hypertrophy of the prostate may simulate a tumor, and in a doubtful case the finding of metastases in the bones or chest may definitely confirm the diagnosis of a tumor of the prostate.

A small tumor of the prostate with little or no urinary symptoms may metastasize early, and roentgenographic examination of the spine or bony pelvis may show metastases as the first evidence of prostatic malignancy. The tumor mass lodges in the venous sinuses of the bones and produces an osteitis, marked osteoplastic activity, and also osteoclastic stimulation (Figs. 9 and 10). The osteoplastic activity, however, being more pronounced, results in considerable formation of bone, usually with wide dissemination and little or no tendency to the formation of discrete nodular tumor masses, as in the case of tumors of the kidney or the thyroid.

It is well known that metastases from the thyroid gland and the urinary tract have frequently been overlooked, particularly in their early stages, because of the fact that a roentgenographic examination of the probable areas of metastases has not been made. Of course, it is impossible to make a roentgenographic examination of the

Fig. 4

Fig. 3
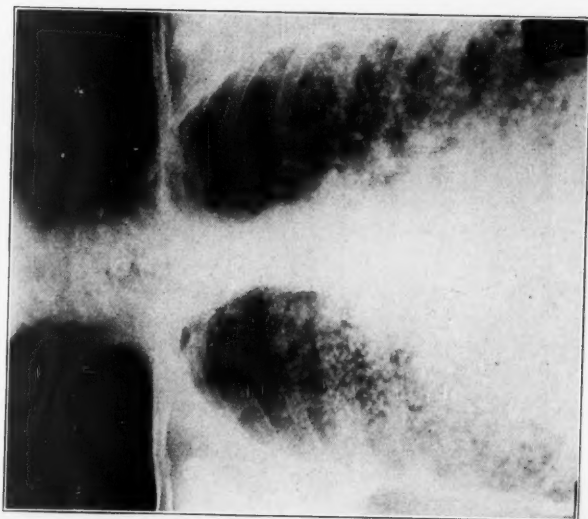
Fig. 6
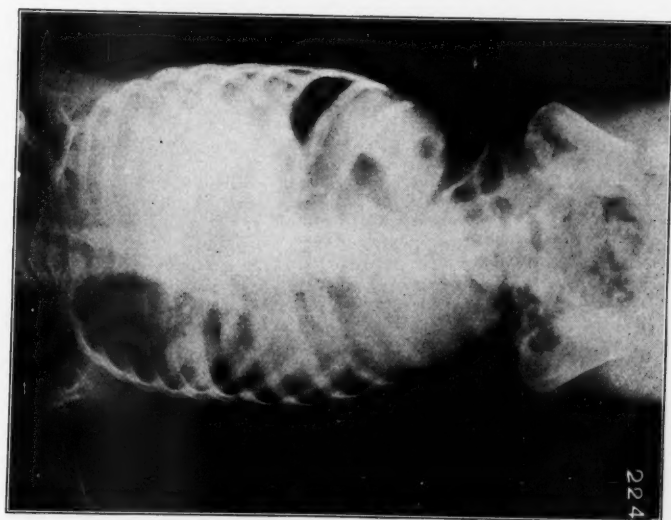
Fig. 5
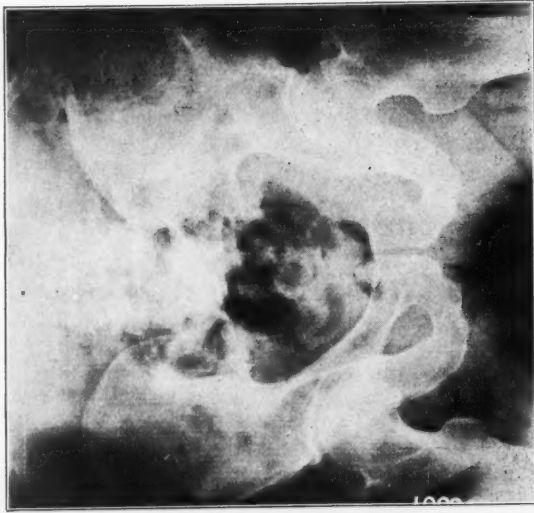
Fig. 8
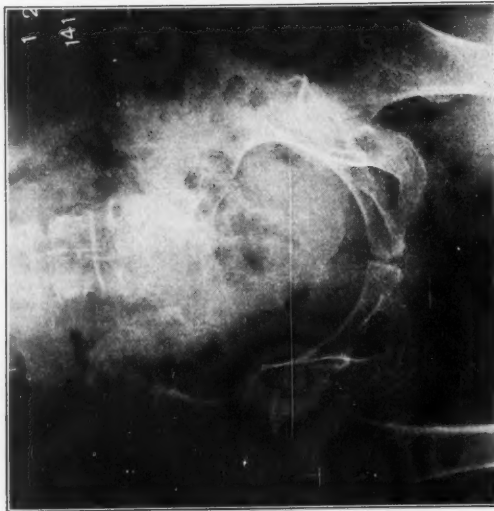
Fig. 7
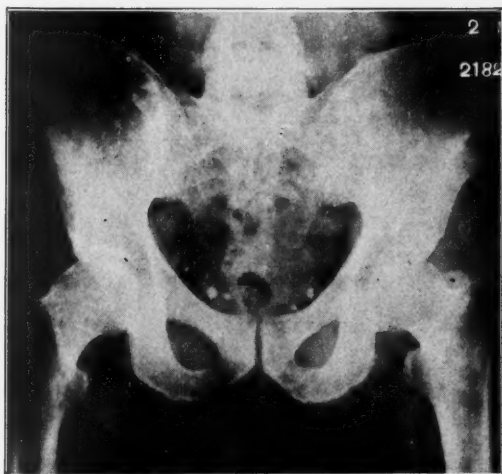
Fig. 9

Fig. 10

entire body in every case of suspected metastases. Therefore it becomes imperative that a knowledge be gained of the areas of the body to which metastases are most likely to extend, and of the order of their frequency. This knowledge is of material aid in making the roentgenographic examination. If metastases are found

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Fig. 11
Roentgenogram showing metastatic destruction of the outer end of the left clavicle from a primary carcinoma of the prostate.

while examinations are being made for other chest or bone pathology, their probable primary focus can also be deduced.

With these ideas in mind, we have made a survey of our cases of metastases from the urinary tract, the prostate gland and the thyroid gland in order to determine the frequency and location of

such metastasis, together with the character of the lesion, in the hope that the roentgenologist could thus render a more efficient service to the clinician and to the surgeon.

It will be at once apparent that in a survey of this kind all cases of metastases can not be represented, as many of these patients die with unrecognized metastatic lesions. We have therefore considered only the areas in which the presence of metastases was definitely determined at the time of the original examination or in a postoperative survey.

Our series includes 268 cases of thyroid malignancy, 55 of which showed metastases. In 34 of these 55 cases the metastases were distributed in the bones and chest as follows:

Chest	22
Pelvis	4
Sternum	2
Clavicle	2
Skull	1
Spine	1
Ribs	1
Knee	1

From these findings it will be seen that the chest is the most frequent site of metastases from the thyroid gland malignancies and that the pelvis, sternum and clavicle are next in frequency.

Of 276 cases of prostatic malignancy, 70 showed metastases to the chest and bony skeleton, distributed as follows:

Chest	5
Pelvis	43
Spine	19
Ribs	2
Humerus	1
Scapula	2
Clavicle	1
Tibia	1
Fibula	2

Of 127 cases of kidney malignancy, 27 showed metastases, 16 of which were in the chest and bony skeleton, distributed as follows:

Chest	11
Spine	2
Skull	1
Ribs	1
Radius	1

Here again it will be seen that the greatest number of cases metastasize to the chest, as in the case of the thyroid.

Summary

In cases of suspected metastases from malignancies of the thyroid gland and the urinary tract, a roentgenographic examination should always be made of the chest first, as being the most likely site of metastases. The pelvis should be examined next and then the lumbar spine. After that, the roentgenologist must be guided in his examination by the evidence of symptoms in the bony skeleton. It must be borne in mind that in cases of metastasis the symptom of pain may be present before the evidence of metastasis can be demonstrated by roentgenographic examination. This is particularly true in the spine, but pain gives the most important information for unusual locations of metastatic lesions in the bony skeleton.

Location of Original Growth	Thyroid	Prostate	Bladder	Kidney
Total Cases in Series......	268	276	340	127
Total Cases with Evident Metastases...........	55	70	15	27
Location of Metastases				
Abdomen..............	1	2	..	..
Bone				
Skull................	1	..	..	1
Spine...............	1	19	1	2
Sternum.............	2	..	..	..
Ribs................	1	2	..	1
Scapula.............	..	2	..	..
Clavicle.............	2	1	..	..
Humerus............	..	1	..	..
Radius..............	..	..	..	1
Pelvis..............	4	43	..	..
Femur..............	..	4	..	..
Knee...............	1	..	..	..
Tibia...............	..	1	..	..
Fibula..............	..	2	..	..
Chest................	22	5	1	11

The above table shows a review of malignancies in the thyroid, the prostate, bladder and kidney, and the frequency with which metastasis was demonstrated by roentgenographic examination.

PROGNOSIS AND TREATMENT OF MALIGNANT GOITER

Robert S. Dinsmore

In a discussion of the prognosis and treatment of malignant goiter it is not pertinent to offer any historical account of the literature pertaining to this subject. In order, however, that the problem may be clearly understood, it is necessary to review the classifications of malignant tumors of the thyroid gland. Although I am fully cognizant of the widely diverging opinions regarding a satisfactory classification of these tumors, I shall present briefly Graham's classification,[1] since it is the one with which I am most familiar and my ideas about treatment and prognosis have been based on such a grouping of the cases.

Graham's classification is as follows:

I. Sarcoma	1. Lymphosarcoma	
	2. Spindle-cell sarcoma	
II. Mixed	3. Carcinoma-sarcoma	
III. Carcinoma	4. Scirrhous carcinoma	not in adenomata
	5. Adenocarcinoma	
	6. Papillary carcinoma	in adenomata
	7. Malignant adenoma	

These various groups may be briefly described as follows:

Lymphosarcoma probably originates in the lymphoid tissue of the thyroid gland. It is a hard, rapidly growing tumor, terminating fatally, usually within a period of months, and in our experience has resisted every type of therapy.

Spindle-cell sarcoma is of infrequent occurrence, and here again in our experience the prognosis is universally fatal. I cannot enter here into any discussion as to whether a true sarcoma may occur within the thyroid gland, but certainly tumors of this type cannot be distinguished from the spindle-cell sarcomata and fibrosarcomata which arise elsewhere in the body. Thyroid tumors of this type are usually recognized clinically as malignant.

It is astonishing to note the rapidity with which sarcomata of the thyroid disappear under x-ray therapy, only to reappear after a few months with the same startling rapidity, when they are unaffected by x-ray.

In a small group of cases we have been forced to classify the tumor as a carcinoma-sarcoma, because both mesoblastic and epithelial elements were present. When tumors of this type are pre-

sented to pathologists, they may be called either carcinoma or sarcoma, and they always excite a discussion. In our experience, the prognosis has been fatal in 100 per cent of the cases.

Scirrhous carcinoma conforms morphologically to scirrhous carcinoma seen elsewhere in the body. Tumors of this type are non-encapsulated and invasive. The prognosis is fatal in 100 per cent of the cases.

Fortunately, tumors of the three types just described are present in only a comparatively small number — approximately 12 per cent — of the cases of malignancy of the thyroid gland.

Adenocarcinoma, not originating in adenoma, represents a group of cases cited here at the Post-Graduate Assembly in 1927, by Graham. These tumors are small, solid, non-encapsulated tumors which appear to have their origin in the non-tumorous portions of an adenomatous goiter. They are always discovered by the pathologist. In gross appearance they resemble adenocarcinoma of the breast. In a series of sixteen cases all patients are living. This is, of course, the most favorable group of the malignancies of the thyroid.

Papillary carcinoma originates in an adenoma. Tumors of this type are encapsulated, are usually cystic and do not metastasize as long as they remain within their own capsules. If they do break through, they may metastasize through the lymph channels, but not through the blood stream — at least metastasis through the latter route has not been noted. These tumors may reach a very large size, as will be noted in one of the cases cited below.

Malignant adenoma is the most important and most frequently encountered type of tumor originating in the thyroid gland. Tumors of this type have given rise to much controversy among the pathologists. Graham has pointed out, as the outstanding characteristics of these tumors, that they invade the blood vessels and metastasize through the blood stream; as in all cases thus classified, this phenomenon has been noted. He also has pointed out that in every case in which recurrence and metastasis followed the removal of an adenoma, invasion of the blood vessels could be demonstrated.

The following cases illustrate the variations in the characteristics and the prognoses and indicate the treatment which may be applied in the presence of different types of malignant goiter.

Case Reports

Case I. The patient was a woman, 64 years of age, who stated that two years before she came to the Clinic her physician had called her attention to the presence of a small nodular enlargement of the thyroid gland in the midline of the neck. At that time the patient had not noticed any symptoms referable to this enlargement, but

a year later she noticed that it had increased in size and at that time she began to have paroxysms of coughing and choking which were relieved by lying down. Two months before her first examination at the Clinic, the gland began to grow very rapidly and caused marked dyspnoea, and pain under the left arm.
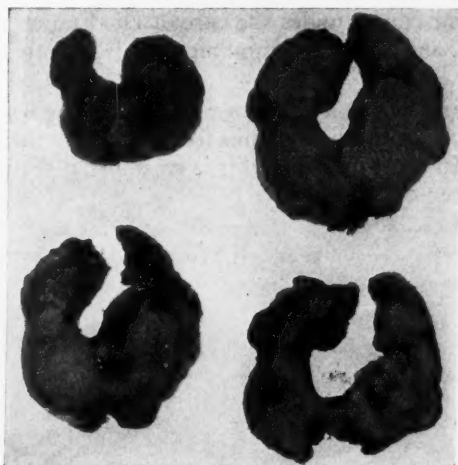
Fig. 1. Specimen: Case I

On examination, there was found to be a very large generalized enlargement of both lobes of the thyroid gland, with considerable thickening of the isthmus. The gland was quite firm throughout, with several large round nodules in the left side, extending from the mastoid to the angle of the jaw, downward toward the clavicle and posteriorly to the trapezious muscle. These nodules, which were freely movable, were thought to be lymph nodes involved in the neoplasm. On the right side of the neck another lymph node was involved, just above the clavicle. The trachea was displaced to the right and the lower border of the gland extended beneath the manubrium and left clavicle. The superficial veins over the upper chest were distended. The impression was that this was a carcinoma of the thyroid gland with metastases to the cervical glands.

On x-ray examination the chest was found to be normal, except for a substernal mass in the upper mediastinum. Laryngeal examination gave no significant findings. The basal metabolic rate was plus 21 per cent.

At operation, which was performed March 29, 1930, there was found to be a moderately hard diffuse enlargement of the whole

gland, which had a yellow-white appearance beneath the capsule. The isthmus was large and fused and completely encircled the trachea. No attempt was made to remove the cervical glands. Histological examination showed this growth to be a lympho-sarcoma. Following the operation, the patient was given a course of x-ray therapy.

The patient is now under the care of Dr. Francis Carter Wood, in New York, and a recent communication from him states that she is still alive.

The unusual feature of this case is that although the tumor was a lymphosarcoma, the patient has lived for more than a year since its removal. In our experience this is an unusual sequel in a case of this type of tumor.

Case II. This patient, a woman 67 years of age, stated that she had had a goiter for 43 years. It remained stationary in size until

Fig. 2. Specimen: Case II

one year before she came to the Clinic, when it began to grow rapidly and became firm in texture. At the time of her examination at the Clinic the patient suffered some shortness of breath and dif-ficulty in swallowing and from local pain which was referred to the head, the right arm and both shoulders. There had been no loss of weight and no cardiac symptoms or symptoms of hyperthyroid-ism. The only positive physical findings were a blood pressure of 174/100 and a very hard nodular mass in the right side of the neck, which involved the isthmus. The clinical impression was that the enlargement of the thyroid was due to a carcinoma. X-ray examina-tion of the chest revealed a substernal goiter. At operation, a very

hard nodular gland was found and a mass about the size of a golf ball was removed. The impression at the time of the operation was that the growth was malignant and that its complete removal was impossible, although the right lobe was completely removed along with the isthmus, and a portion of the left lobe.

This patient was given x-ray therapy, but only lived for about six months.

The pathological report was fibrosarcoma.

Case III. The patient was a woman, 71 years of age, who five years before she came to the Clinic first noticed a small firm nodule
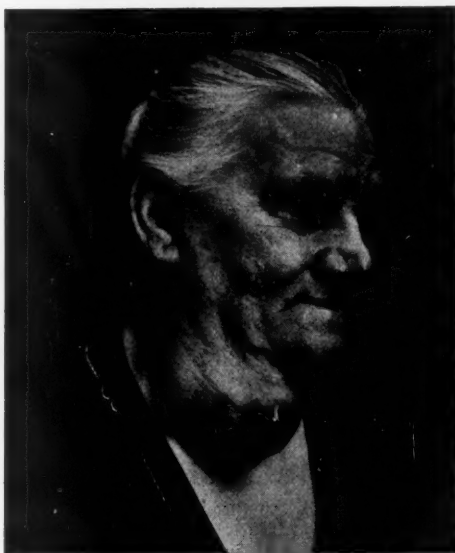
Fig. 3. Case III

in the right side of the neck. This had increased in size steadily, the greatest increase occurring during the preceding year. Four weeks before, the mass had become dark in color and soft in consistency and broken down, and a small amount of fluid had drained from it. There had been no pain or tenderness and the symptoms had always been referred to the local growth.

The only positive findings in the physical examination were a blood pressure of 224/116, and a very large irregular nodular enlargement on the right side of the neck, extending from the clavicle

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to about two centimeters from the mandible. There were several soft areas on the anterior surface of the tumor. The gland was removed and the tumor found to be a papillary adenocarcinoma. The patient was given postoperative x-ray therapy and has now lived for more than two years, but at the present time there is a recurrence in the area of the operative wound.

Case IV. The patient was a woman, 42 years of age, who was first seen at the Clinic on January 13, 1928. Her chief complaint was goiter, with swelling of the face and shortness of breath. The patient stated that she had had a goiter for several years, but that it had recently begun to increase in size. During the preceding two weeks, shortness of breath, puffiness of the face and some duskiness of the skin had developed. She had also noted a bluish discoloration of the chest and some pain.

On physical examination the patient was found to have a dusky, puffy face, large veins over the anterior chest and a very large, hard, diffuse enlargement of the thyroid which extended well down below the sternum. The clinical diagnosis was colloid goiter with obstruction. X-ray examination revealed a large intrathoracic goiter, extending down into the mediastinum, one-half of the way into the chest.

At operation, on January 17, 1928, a large, hard, firm, fixed gland was found which extended well down into the mediastinum. The gland gave the appearance of a malignancy. I decided that it would be futile to attempt to remove the entire growth, the indications being for decompression of the trachea and later x-ray treatment.

I removed a considerable portion of the left lobe and noted at the time that on the surface of the growth there was a large, dilated, thin-walled vein, through the walls of which could be seen masses of tissue which were probably malignant, and which had broken through the wall of the vein and were being carried into the general circulation. We felt that in all probability this patient had distant metastases. The ribbon muscles were clamped on both sides and cut transversely and not reapproximated. The pathological diagnosis was malignant adenoma and study of the tumor showed many vessels with blood vessel invasion.

The patient was given x-ray therapy and at the end of the eight weeks' period practically all of the symptoms of obstruction had disappeared and her condition was highly satisfactory. However, she died approximately six months after her first admission.

Case V. The patient was a woman, 44 years of age, who first came to the Clinic in January, 1927. She stated that she had always

had a full neck, but was quite insistent that the tumor then present had appeared with the preceding three months.

On physical examination, the patient was found to have a movable tumor which felt cystic, and gave the impression that there had been a hemorrhage into an adenomatous cyst.

At the time of operation, however, the tumor was found to be completely filled with neoplastic tissue and the pathological diagnosis was malignant adenoma.

A course of x-ray therapy was given, but the patient returned in
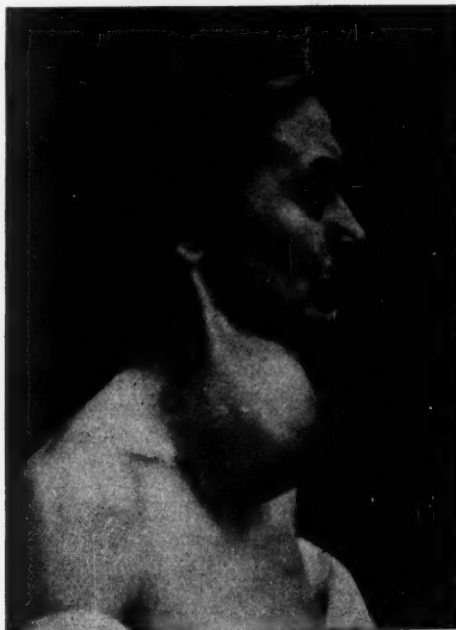
Fig. 4. Case V

three months with a recurrence in the incision line, which was removed. This was found to have cells of the same type as those noted in the previous operation. Another course of x-ray therapy was given.

The patient returned from time to time and was found to be rapidly losing weight. X-rays were taken for the purpose of discovering whether or not there were any metastatic lesions, but with the possible exception of a lesion in the left humerus, none were found.

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The patient became very much emaciated and I felt that she certainly had generalized metastases which we were unable to locate. She died about eighteen months after the primary operation. Before death, a large hard tumor appeared on the side of the face. This apparently was in the parotid gland.

Case VI. The patient was a woman, 53 years of age, who was first seen on February 13, 1928. She complained of a goiter, which,

Fig. 5. Case VI

though she had had it for more than thirty years, during the preceding year had been growing rapidly and had doubled in size. The patient was nervous and irritable, had a marked tremor and had lost twenty pounds in weight. Her heart was rapid and she was dyspnoeic. There was also a history of pain in the epigastrium and of other symptoms suggesting the presence of a duodenal ulcer.

On physical examination a large adenoma on the right side of the neck was seen. This was freely movable and smooth. Our clinical

impression was that the patient had an adenoma with hyperthyroidism and duodenal ulcer, and it was considered probable that the adenoma was malignant.

The x-ray examination revealed the fact that the trachea was displaced well to the left and was compressed. When the tumor was removed, it was found to be a malignant adenoma and many veins were found to be filled with the tumor tissue.

The patient was given x-ray therapy. At the last report, two years after her operation, she was living and well.

In this case, a goiter of long duration, which showed rapid recent growth, was accompanied by the well-defined symptoms of hyperthyroidism which are seen in a high percentage of cases — 37 per cent, according to Coller.

Case VII. The patient was a man, 67 years of age, who came to the Clinic because of a swelling of the neck which had been first noticed ten years previously on the right side. This had gradually increased in size, especially during the preceding year and was apparently pressing on the trachea. The only other subjective symptoms were nervousness and a fluttering of the heart.

On physical examination, a large nodular, hard, irregular tumor on the right side of the neck was found. There was moderate arteriosclerosis and some irregularity of the heart, with an occasional dropped beat.

Laryngeal examination and x-ray studies of the chest revealed nothing of significance.

A clinical diagnosis of malignant goiter was made. It was thought that the tumor could probably be removed *in toto*, together with a block dissection of the glands of the neck. At operation, however, a very large tumor, with multiple masses, was dissected out, but it was impossible to remove the whole mass, as a very large, hard extension descended under the clavicle on the right side.

At this time the condition was considered to be almost hopeless, but the patient was given x-ray therapy, with the result that within a very short time the mass in the neck practically disappeared. The large glands which were present in the neck, which have become round, hard nodules, have remained stationary in size up to the present time — that is, for eight years.

This case is presented because in spite of its apparent hopelessness, being a malignant adenoma with marked extension and multiple masses, there has been a most satisfactory clinical result.

Case VIII. The patient was a man, 46 years of age, who came to the Clinic with a large tumor on the right side of the neck which had extended to the left of the third rib on the right side. In January,

1916, the tumor was removed, some difficulty being encountered in dissecting it from the thorax. The space left by the tumor became entirely obliterated by the pleura and the marked engorgement of the veins of the neck disappeared. The pathological report of the time of this operation was malignant adenoma.

Seven years later (June, 1923) the patient returned with a tumor in the right lower pole, about the size of a small hen's egg. This was removed and found to be a tumor of exactly the same type as that

Fig. 6. Case VIII

removed at the primary operation. The patient was observed from time to time, but returned again in September, 1923, with another recurrence. At this time a mass occupied a position higher up in the neck adjacent to and including the sternocleidomastoid muscle. This mass was removed, together with a large portion of the muscle. The diagnosis at this time was again malignant adenoma.

In April, 1925, the patient again returned with a mass about the size of a large marble on the left side, lying just posterior to the sternocleidomastoid muscle, extending deeply into the neck and

firmly attached to the surrounding tissues. This mass was carefully dissected from the carotid sheath.

In September, 1928, a small nodule was removed from the level of the left sternoclavicular joint. The same type of neoplastic tissue was again found within the capsule.

In October, 1928, two small nodules were removed from the skin above the scar on the left side.

In March, 1930, he returned with a small recurrence on the right
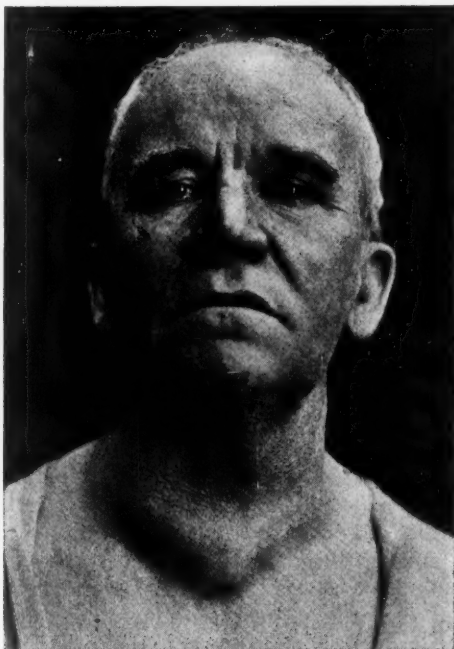
Fig. 7. Case IX

side of the neck anteriorly, near the midline. This tissue was also removed and the same pathological picture noted.

After each operation, the patient was given a course of x-ray therapy. This case is peculiarly interesting, because it presents a patient who has now lived for more than fifteen years, has had seven operations and seven courses of x-ray therapy, and throughout this period has been an active, practically well individual.

Case IX. The patient was a man, 63 years of age, who came to the Clinic on March 26, 1927, complaining of a hard tumor in the

neck, dyspnoea and the coughing up of blood. He stated that seven years previously he had first noted a small hard tumor in the neck just below the cricoid cartilage. This had remained stationary for three or four years and then began to grow larger, extending laterally to the right side of the neck. During the preceding six months, its growth had been quite rapid. Three months before the patient began to cough up bright blood, very little during the day, more at night. He had lost no weight, his appetite was good, but he felt that he had become somewhat more nervous.

On physical examination a very hard tumor was found in the isthmus of the thyroid, extending into the right lobe. It was stony hard but movable. The breath sounds over the chest were distant, but otherwise the physical examination disclosed nothing of significance.

It was our impression that this was a malignant tumor of the thyroid gland. Examination of the larynx showed some thickening of the cords and reddening, but both cords were movable. X-ray examination of the chest showed advanced metastases in the lungs. The patient was given x-ray therapy, however, and on May 2, 1927, there was apparent improvement, although the findings remained the same. He returned again on June 6, 1927, when it was found that the tumor had become markedly smaller in size, that the lesions in the chest were less marked, and that the general condition of the patient had improved. The x-ray films also showed some improvement in the lungs.

On August 25, 1927, there was considerably more improvement, but when the patient returned in December, 1927, metastases were noted in the ribs, although the general condition was fairly good. Surprisingly enough, this patient survived for twenty-six months after the initial diagnosis was made. This case suggests the question as to whether or not a patient with a malignant tumor in the thyroid gland and obvious metastases in the chest should be treated. We feel that they should, for certainly the marked physical improvement noted in this case and the comfort of the patient during the time he lived justify the procedure.

Case X. The patient, a woman 64 years of age, had had a thyroidectomy performed in 1920 by Dr. Crile and she came to the Clinic five years later with a large ulcerating mass in the neck. She stated that the incision following the thyroidectomy had never healed and that constant drainage had been present.

Upon physical examination, the patient was found to have a large, fixed mass in the neck, over the anterior surface of which was a large fungating ulcer. For the most part this tumor had been pain-

less and the patient had had few other symptoms than those presented by the local lesion.

The patient died shortly after her examination here. I think the interesting point about this case is the fact that a malignancy of the thyroid had persisted for more than five years, presenting few symptoms other than those from the local lesion.

· *Case XI.* The patient, a woman 72 years of age, stated that she had had a goiter for many years; fourteen years before it had begun

Fig. 8. Case X

to enlarge and had grown steadily since that time. Two years before an abscess developed which was opened, and the patient experienced a great deal of relief. This abscess had continued to drain and the patient had also had difficulty in swallowing.

Several x-ray treatments had been given prior to the patient's examination at the Clinic.

There were no significant findings in the physical examination, save for the tumor in the mid-line of the neck, which was very hard

and fixed. It was red in color and there was a sinus in the central portion, from which there was a slight drainage.

Laryngeal examination revealed that the entire left pharyngeal wall, including the tonsil, had been pushed to the right side by an extrinsic growth, the left pharyngeal wall coming in contact with the opposite side. The epiglottis was also pushed forward on the base of the tongue. It was absolutely impossible to see any of the laryn-

Fig. 9. Case XI

geal structures. The mucous membranes over the tumor were intact and there was no ulceration. The breathing space was small.

Due to the hopelessness of the patient's condition, and the fact that she had had recent x-ray treatment, she was not given any x-ray treatment at the Clinic.

The patient died about two months after this examination.

Case XII. The patient, a woman 71 years of age, stated that she had had a goiter on the right side of her neck since the age of five or six years, and that from year to year this had increased slight-

ly in size, but that during the preceding summer it had grown very rapidly on the left side. The patient complained of some dyspnoea, some nervousness and loss of weight.

Examination revealed a markedly enlarged, very firm thyroid in the left side of the neck. It was not movable, but was fixed and presented hard nodules, apparently arising for the most part from the left lobe. There was also a mass about the size of a pigeon's
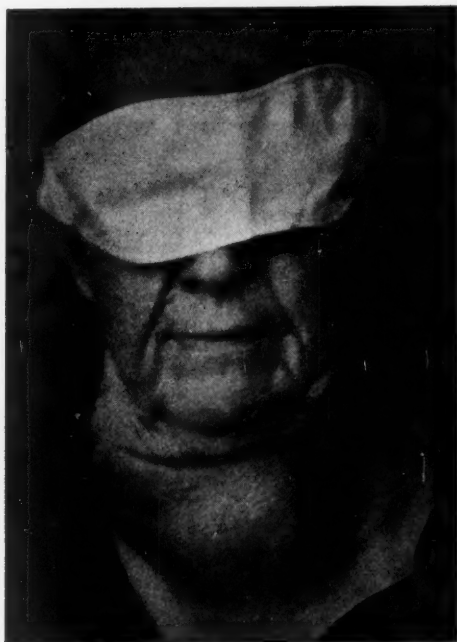
Fig. 10. Case XII

egg in the inframandibular region in the midline. The case was considered inoperable and the patient was given x-ray therapy.

She returned in two months much more comfortable and the mass was found to be smaller in size, but the patient died less than a month later.

Case XIII. The patient, a woman 64 years of age, stated that she had always had a goiter and that nine months before she came to the Clinic a new lump had appeared within the tumor, which had been removed, but the whole mass had grown very rapidly in size during the past few months. This very hard, firm, fixed mass presented areas which were apparently broken down and were fluctuant.

In this case, of course, the condition was absolutely hopeless. It is typical of the group of cases in which the patient allows the tumor to reach an enormous size before seeking advice.

GENERAL CONSIDERATIONS

From the cases described above, it would appear that we must reconsider our former impression that in all cases of malignancy of the thyroid gland the prognosis is bad. While it is true that in the first four groups cited there is a mortality of approximately 100 per cent, we must remember that these groups comprise only about 12

Fig. 11. Case XIII

per cent of the total number of cases of malignant goiter. I fully agree with Coller[3] and Pemberton[5] in their statements that the prognosis is better than is generally supposed, for we have many patients who have lived for a long period of time.

In his textbook, Waring[2] reports a case of carcinoma of the thyroid with cervical gland involvement which had remained well for twenty-one years and cited a case of Breitner's in which three operations, each including a tracheotomy, had been performed. The patient lived for more than a ten-year period, and at the time of this report was 66 years of age.

Obviously, there is a group, illustrated by the last cases cited, in which no hope of aid can be extended to the patient, in which cases the growth has extended into the larynx or in which massive metastasis has taken place. On the other hand, we are seeing cases which at the time of operation or of x-ray therapy have been considered hopeless, in which the patients have now lived many years.

It is also important to remember that when there is a recurrence the case should not always be considered to be hopeless, but that the tumor should again be extirpated and x-ray therapy again applied. Metastasis in the chest also should be treated with x-ray therapy, as this measure may add comfort and length of life to the patient.

In certain cases it is quite evident that any operative procedure is unjustified. It is true also that a diagnosis can be made with a reasonable degree of certainty in less than 50 per cent of the cases.

The ideal procedure, of course, is to remove the entire tumor. In these cases, the utmost care must be exercised, for I have seen instances in which a wide dissemination of the neoplastic tissue by embolism has occurred immediately following the manipulation incident to the operation.

But the question arises as to whether or not any plan of management can apply to the whole group. One important point is to ascertain whether or not the tumor is confined within the neck, that is, whether or not metastasis has taken place in any place other than in the cervical glands. For this reason, an x-ray examination of the chest should be a routine procedure, together with a careful examination of the long bones. Laryngeal examination is also important, as it is necessary to know whether extension has taken place in the larynx and whether or not the vocal cords are paralyzed. The paralysis of either or both vocal cords is important from the diagnostic standpoint, as it has been our experience that vocal cord paralysis very rarely occurs in cases of non-malignant goiter, other than thyroiditis.

Additional information can sometimes be obtained from an x-ray examination of the neck, which may disclose a cyst with a calcified wall or a calcified adenoma. It has been my personal experience that cysts with calcified walls have been the most frequent source of error in the differential diagnosis of tumors suspected of being malignant tumors.

In cases of obstruction it may be necessary to perform a so-called decompression operation, and in the absence of vocal cord paralysis this procedure often affords great relief. This operation includes a wide transverse incision, through all the preglandular muscles,

ligation of the vessels in the cut ends of the muscles and closure of the subcutaneous tissues and skin over the tumor. In like manner the removal of a portion of the tumor often results in great relief from pressure on the trachea.

In other cases, an immediate tracheotomy is required. In certain cases this operation may be technically difficult. When the tumor is large and completely covers the trachea from the substernal notch to the cricoid, it may be astonishingly difficult to find the trachea and, having found it, to recognize it, as it may be a small cord-like structure.

We have had little experience with the use of radium in these cases but rely upon x-ray therapy. We are constantly using x-ray therapy in all types of malignant tumors, but it has been of little aid in the cases of sarcoma, carcinoma-sarcoma and scirrhous carcinoma. The sarcomas, to be sure, do respond with rapidity to x-ray, but recur rapidly. In cases of small adenocarcinoma, not originating in adenomata, we do not feel that x-ray therapy is indicated and we do not advise its use, unless these tumors are on the surface of the gland and have become adherent to the trachea or the preglandular muscles. In the largest group of malignant tumors of the thyroid gland — malignant adenomata and papillary carcinomata — we certainly feel that the results are now more encouraging than we had supposed possible before the advent of the improved technic in x-ray therapy.

I feel, as Clute[4] does, that a biopsy should be done whenever possible. As he points out, by this means a diagnosis can be established and the type of malignancy revealed, this in turn making it possible to determine the probable duration of life and response to x-ray therapy.

CONCLUSIONS

From the series of cases here presented, the following conclusions may be drawn:

1. The prognosis in cases of malignant goiter depends first upon the type of tumor, and, second, upon its extent.

2. In cases of sarcoma (20 cases) the results have indicated that the duration of life is short, as every patient, with two exceptions, has died within a short time.

3. A like prognosis must be made in cases of sarcoma-carcinoma (5 cases) and of scirrhous carcinoma, which are always fatal.

4. In cases of adenocarcinoma which do not arise from tumorous tissue, the prognosis is favorable. We know of no case in which death was due to this cause.

5. The foregoing four groups fortunately represent only 12 per cent of the malignant tumors of the thyroid gland. The remaining 88 per cent offer a prognosis which is much more encouraging than is generally supposed.

6. Papillary carcinomata treated by combined surgery and x-ray give a 50 per cent three-year cure, and malignant adenomas a 25.8 per cent three-year cure.

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RIEDEL'S STRUMA IN CONTRAST TO STRUMA LYMPHOMATOSA

Allen Graham

In 1896[3] and 1897[5] Riedel reported three cases of a peculiarly hard, indurated, infiltrating lesion of the thyroid which clinically and at operation was thought to be a malignant neoplasm, but was interpreted pathologically to be a chronic inflammatory process. The non-neoplastic nature of the lesion and its benignancy seem to have been confirmed by the clinical course of the disease following incomplete surgical removal of the lesion. The definitive cause of the process was not determined. The consistency of the tumefaction was compared to that of iron, and this physical feature gave rise to one of the terms, "eisenharte strumitis," which was applied to these cases by Riedel and by subsequent writers.

During the discussion that followed the presentation of Riedel's first two cases, Cordua[4] mentioned his experience with a similar case, that of a female 13 years of age. Additional data concerning this case were furnished to Tailhefer[6] in a personal communication from Cordua. The details, however, were never published, according to Riedel[5] (1910); hence the case is of little statistical value except for the facts as to age and sex.

In the fifteen years succeeding Riedel's original publication, cases of similar nature were reported under various titles by Tailhefer[6] (1898): ("inflammation chronique primitive, canceriforme"); Ricard[11] ("degenerescence fibreuse du corps thyroide"), (1901); Berry[15] ("primary chronic inflammation"), (1901); Silatschek[19] ("eisenharter strumitis"), (1910); Spannaus[20] ("Riedelsche struma"), (1910); Delore and Alamartine[21] ("thyroidite ligneuse"), (1911); Sebileau[22] ("ligneous thyroiditis"), (1911), and Murray and Southam[24] ("ligneous thyroiditis"), (1912).

It is well to pause and consider this small group of cases, reported by several different authors from three different countries, for if there is any justification for dignifying these and subsequently reported cases by the name of Riedel's disease or ligneous thyroiditis, with the implication that they constitute an entity, as opposed to any other sort of chronic thyroiditis of unknown or non-specific etiology, this justification is to be found in a study of the case records as a whole and in series. The entity of the disease cannot be established by singling out any particular feature of the individual cases, because up to the present time no pathognomonic indication of Riedel's disease, either clinically or pathologically, has been discovered.

That the foregoing is not an overstatement has been amply demonstrated by the diversity of interpretation by recent writers of the cases previously published; by the fact that no two writers accept and list the same cases in their reviews, and by the further fact that cases in which well established and well recognized pathological changes in the thyroid are associated with the greatest variety of clinical conditions have been and are being reported as instances of Riedel's disease under the guise of chronic or ligneous thyroiditis.

If we assume that Riedel's disease is an entity, it seems to me that there is no possibility of reconciling many cases reported and cited as Riedel's disease since 1912 with those reported prior to that date. The latter cases present a striking uniformity of clinical symptoms, physical signs, operative findings, pathological changes in the thyroid, involvement of surrounding structures, and postoperative course. Moreover, in all instances these cases are characterized by an extension beyond the thyroid, which leaves no grounds for quibbling, by malformation of one or both lobes of the thyroid beyond the possibility of recognition as an organ or gland, and by the absence of a known etiological factor in each case. The available data do not indicate that the onset of the disease was preceded by hyperthyroidism in any case, nor did spontaneous suppuration occur. In no instance can it be seriously maintained — and certainly it has not been demonstrated — that the thyroid was the seat of tuberculosis, syphilis or a neoplastic process. There is rather universal agreement that the lesion is in the nature of a chronic inflammatory process. If these be the criteria of Riedel's disease, more than 50 per cent of the cases appearing in the literature should be reclassified.

The objection may and doubtless will be raised that the cases cited thus far represent the end stage of the process. This may or may not be true. My only intention is to point out and emphasize that at least the end stage is well known. Any process proposed as representing the incipient or intermediate stage should logically tend to progress to the end stage, it should not be inconsistent with what we know of the disease in all its aspects, and it should admit of no other interpretation if it is to be considered as an entity. These conditions, we believe, have not been realized up to the present time.

In 1912 Hashimoto[26] reported four cases which he designated "Struma lymphomatosa," all in women forty years of age and over, who presented few and relatively insignificant symptoms, associated with uniform bilateral enlargement of the thyroid. The onset

of the disease was insidious and its progress was slow. The enlarged thyroid gland was firm to hard in consistency (in one case malignancy was thought to be present); at operation the gland was found to be adherent to the trachea but not to the surrounding structures. In these four cases, both lobes were resected without great difficulty, except for bleeding in two cases, and no serious post-operative complication occurred. Recovery was slow in all cases, but was complete within from twelve to eighteen months. Two of the patients developed symptoms suggestive of post-operative hypothyroidism, and a third was treated for this condition by the administration of thyroid preparations. Pathologically the glands were found to be extensively infiltrated by lymphocytes, both diffusely distributed and in localized collections, and in all cases the glands contained numerous lymphoid follicles with germinal centers. Varying degrees of fibrosis and atrophy and hypertrophy of the glandular tissue were recorded. In Hashimoto's cases, as in those reported by Riedel, there was no indication that hyperthyroidism, hypothyroidism, suppuration, tuberculosis, syphilis or neoplasm were factors in the etiology. The exact nature of the condition was not determined, but Hashimoto came to the definite conclusion that his cases were not in the same category with Riedel's. It is a singular fact that no other cases have appeared in the literature under the title of "struma lymphomatosa," so far as I am aware. In association with Dr. E. P. McCullagh,[61] I have recently reported four cases of a similar nature and we are in general agreement with Hashimoto's conclusions.

Numerous authors have suggested and have apparently accepted the opinion that struma lymphomatosa is the early stage of Riedel's disease. A few have dissented. Heineke[30] (1914) did not believe that the two conditions were identical. Reist[39] (1922) seemed to make certain distinctions between them. Perman and Wahlgren[50] (1927) stated that, in their own case at least, Riedel's disease was not necessarily preceded by struma lymphomatosa. At the first operation a small, white, hard nodule, in no way suggestive of struma lymphomatosa, was removed from the lower pole of the right lobe. Seventeen months later, at the second operation, both lobes were diffusely involved and the findings were characteristic of Riedel's struma.

The writer, likewise, is of the opinion, based on a study of Hashimoto's four cases, four reported by Graham and McCullagh,[61] and cases which I now believe can be identified in the literature, that Riedel's struma is not necessarily preceded by struma lymphomatosa; that struma lymphomatosa does not necessarily progress

to Riedel's struma; and that it is highly improbable that there is any necessary relationship between these two conditions.

If the foregoing observations can be substantiated, it would seem more logical to separate the two groups, collect and report more complete data, and trust to further experience to determine the exact status of these two relatively rare lesions, presumed by some to be entities and by others to be non-entities. The latter is the only possible conclusion that can be drawn from a study of the cases reported in the literature up to the present time.

In support of this position, a summary of the results obtained from a recent study of the literature is submitted. This is not presented as a complete review of the literature, but it is believed that the original sources of information have been examined, relative to at least 90 per cent of all cases reported or cited as Riedel's struma, ligneous thyroiditis, woody thyroiditis, Hashimoto's disease, struma lymphomatosa and chronic thyroiditis, when there has been an implication of relationship to either Riedel's struma or struma lymphomatosa.

From 82 original publications, 104 cases have been collected which are listed in Table 1. The year, the author, the author's interpretation and the number of cases reported or cited are indicated in their respective columns. The small columns to the right indicate my disposition of the 104 cases for the purpose of the present paper, which is to *contrast the type of lesion reported by Riedel with the type of lesion reported by Hashimoto*.

Group 1 — Acceptable as Riedel's struma (41 cases).

Group 2 — Acceptable as Hashimoto's struma (24 cases).

Group 3 — Adenomata with inflammation and fibrosis (8 cases).

Group 4 — Cases of hyperthyroidism (2 cases).

Group 5 — Atrophy and fibrosis, not compatible with groups 1 and 2 (3 cases).

Group 6 — Suppuration in the thyroid (5 cases).

Group 7 — Tuberculosis of the thyroid (1 case).

Group 8 — Syphilis of the thyroid (3 cases).

Group 9 — Unverified by examination of tissue (6 cases).

Group 10 — Insufficient data (11 cases).

It should be borne in mind that all the cases listed in Table 1 have been reported or cited as instances of Riedel's disease. The groups indicate clearly although not completely the great variety of clinical diseases and pathological processes that have been reported as Riedel's struma.

TABLE I

A List of 104 Cases Reviewed

Year	Author	Reported as	Number of Cases	1	2	3	4	5	6	7	8	9	10
				Writer's Interpretation and Grouping for Statistical Purposes — Group No.									
1883	Wolfler	Multiple Fibromata	1			1							
1885	Bowlby	Infiltrating Fibroma (? sarcoma)	1	1									
1896	Riedel	Eisenharte Strumitis	2	2									
1896	Cordua	In discussion	1										1
1897	Riedel	Chronic Strumitis	1	1									
1898	Tailhefer	Chronic Primary Thyroiditis (Canceriforme)	1	1									
1898	Riedel	Cited by Tailhefer	1										1
1898	Kuttner, Case 2	Struma syphilitica	1	1									
1899	Loewy et Loeper	Tumeur Fibreuse du Cou	1	1									
1900	Viannay	Strumitis	1						1				
1901	Ricard	Fibrous Degeneration	3	1									2
1901	Berger	In discussion	1									1	
1901	Walther	In discussion	2									2	
1901	Poirier	In discussion	1									1	
1901	Berry	Chronic Thyroiditis	2	1		1							
1902	Ourmanoff	Fibroma of Thyroid	1	1									
1904	Genet	Compression vena cava	1						1				
1909	Poncet et Leriche	Inflammatory tuberculosis and the thyroid gland	1							1			
1910	Silatschek	Eisenharte Strumitis	1	1									
1910	Spannaus	Riedel's Struma	1	1									
1911	Delore et Alamartine	Ligneous Thyroiditis	1	1									
1911	Sebileau	In discussion	2	2									
1911	Barjon	Ligneous Thyroiditis	1									1	
1912	Murray and Southam	Ligneous Thyroiditis	1	1									
1912	Vogel	Strumitis	1			1							
1912	Hashimoto	Struma Lymphomatosa	4		4								
1912	Poncet et Leriche	Syphilis of Thyroid	1								1		
1913	Meyer	Thyroiditis Chronica Maligna	1	1									
1913	Simon	Riedel's Struma	1	1									
1914	Heineke	Chronic Thyroiditis	2	2									
1914	Tomaselli	Ligneous Thyroiditis	1						1				
1914	Wrede	Eisenharte Strumitis	1	1									
1915	Brunger	Chronic Thyroiditis	3				2	1					
1918	Balfour	Riedel's Struma	1										1
1920	Berry	Chronic Thyroiditis	3		2	1							
1921	Nicholson	Woody Thyroiditis	1	1									
1921	Kleinschmidt	Eisenharte Struma	1	1									
1922	Monod	Ligneous Thyroiditis	3	1							2		
1922	Reist	Chronic Thyroiditis	6		4	2							
1922	Mysch	Riedel's Struma	1						1				
1922	Erkes	Riedel's Struma	1	1									
1924	Bohan	Ligneous Thyroiditis	1	1									
1924	St. George	Chronic Productive Thyroiditis	3	2				1					
1925	Shaw and Smith	Riedel's Chronic Thyroiditis	6		4	1		1					
1925	Meeker	Riedel's Struma	1		1								
1925	Hahn	Non-suppurative Chronic Thyroiditis	1			1							
1926	Smith and Clute	Ligneous Thyroiditis (Riedel)	5		5								
1926	Grunberg	Chronic Thyroiditis	1	1									
1926	Searls and Bartlett	Thyroiditis (Riedel)	2										2
1927	Perman and Wahlgren	Chronic Thyroiditis (Riedel)	1	1									
1927	Tucker and Gertz	Chronic Thyroiditis (Riedel)	1	1									
1927	Schultz	Riedel's Struma	3										3
1927	Matthews	Woody Thyroid	1	1									
1928	Mallet-Guy, Barbier and Heitz	Chronic Ligneous Thyroiditis	1	1									
1928	Johnson	Thyroiditis	1									1	
1929	Wingate	Chronic Thyroiditis (Riedel)	2	1	1								
1929	Heyd	Benign Granuloma (Riedel)	2	1									1
1929	Kent	Chronic Thyroiditis (Riedel)	2	2									
1929	Hellner	Eisenharte Strumitis	1	1									
1929	Maloney	Ligneous Thyroiditis (Riedel)	3	1		1			1				
1931	Graham and McCullagh	Struma Lymphomatosa	4			4							

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Pertinent data relative to Groups 1 and 2 are summarized in Table 2. Groups 3 and 5 will be discussed in a separate communication in the near future.

The contents of Table 2 do not and are not intended to establish as an entity either Riedel's struma or struma lymphomatosa. Little support, however, is to be found for the view that these two are interdependent or interrelated conditions. The indications are strongly in the other direction.

The incidence with reference to age and sex is striking and is probably not without significance. In Group 1, 41.5 per cent of the patients were males and 58.5 per cent were females. In Group 2 only 4.2 per cent were males and 95.8 per cent were females. In Group 1 the youngest patient was 23 years of age, the oldest 64; the mean age was 43.5 and the average age was 36.2. In Group 2 the youngest patient was 40 years of age; the oldest 75; the mean age 57.5 and the average was 52.4. It is worthy of note that the youngest patient in the Hashimoto group was older than the patient of average age in the Riedel group. That the average age of patients in a group of cases presumed to represent the early stage of a process is greater than the average age in a group presumed to represent the end stage is indeed a strange coincidence.

The average duration of symptoms (when symptoms were present at all in the Hashimoto group) was somewhat greater in Group 2 than in Group 1.

The duration of the goiter was slightly greater in the Hashimoto than in the Riedel group. While the difference is not great, it indicates that, although the average duration of the Hashimoto struma (said to be the early stage) may be as great or greater than the average duration of Riedel's struma (said to be the end stage), in not one of the twenty-four cases of the former type did the disease progress to anything approaching the picture presented by Riedel's cases.

The thyroid involvement was bilateral in approximately 50 per cent of cases in Group 1 and in 100 per cent in Group 2. If Riedel's struma is preceded by struma lymphomatosa, one lobe must have regressed remarkably in 50 per cent of the cases in Group 1.

Diffuse cervical cellulitis was present in 78 per cent of cases in the Riedel group and entirely absent in those in the Hashimoto group. The most that can be affirmed in regard to the latter group is that in some cases the capsule of the gland was adherent to surrounding muscles. Adhesions of equal extent occur frequently in cases of exophthalmic goiter.

TABLE 2

Comparison of Riedel's and Hashimoto's Struma

		Group 1 41 Cases Riedel Type	Group 2 24 Cases Hashimoto Type
Sex	Male	17 (41.5%)	1 (4.2%)
	Female	24 (58.5%)	23 (95.8%)
Age	Youngest	23 years	40 years
	Oldest	64 years	75 years
	Mean	43.5 years	57.5 years
	Average	36.2 years	52.4 years
Duration of Symptoms	Shortest	15 days	30 days
	Longest	2 years	6 years
	Average	7.3 months (26 cases)	1.2 years (14 cases)
Duration of Goiter	Shortest	30 days	3 days
	Longest	3 years	6 years
	Average	1 year (28 cases)	1.3 years (16 cases)
Hyperthyroid	Preoperative	none	none
Hypertension	Preoperative	none	5 (20%)
Clinical Diagnosis	Malignant	20 � 90%	6 � 55%
	Malignant?	8 ⎭	5 ⎭
	Benign	4	9
	Not stated	9	4
Thyroid Involvement	Bilateral	51.4%	100%
	Unilateral	48.6%	none
Operative Findings	Diffuse	78.0%	----
	Cervical	----	none
	Cellulitis	----	----
Operation	Completed	22.2%	54.2% (2 lobes)
	Incomplete	51.2%	41.7% (1 lobe)
	Abandoned	17.0%	none
	Biopsy only	9.8%	4.2%
	Tracheotomy	22.2%	none
Hypothyroid	Postoperative	19.0% (32 cases)	58.0% (19 cases)
Deaths	Postoperative	4	none
	Later	2	none

In 90 per cent of the cases in the Riedel group a diagnosis of malignant goiter was made, or maglignancy was suspected and could not be ruled out. In only 55 per cent of the Hashimoto group was the lesion diagnosed as malignant or suspected of being malignant.

Postoperative hypothyroidism occurred in 58 per cent of the Hashimoto group and in only 19 per cent of the Riedel group.

In Group 2 no deaths were recorded. In Group 1 four patients died following operation while in the hospital, and two died after being discharged from the hospital. The data concerning the end results are rather meagre, however, in both groups.

Operative and postoperative complications in the Hashimoto group were practically nil, while both the operative and postoperative complications in the Riedel group make a distressing record. These complications include division of the clavicle, resection of the manubrium, resection of the jugular vein, carotid artery, vagus

and recurrent nerves, injury to the esophagus, injury to the thoracic duct, hemiplegia, panophthalmitis, and numerous tracheotomies. None of these complications occurred in the Hashimoto group.

Without going into further detail, I believe that the data which have been summarized justify the opinions which I expressed earlier in the paper.

Nothing has been said concerning the pathologic histology in either group. I believe that too great reliance upon the microscopical findings and too little attention to the clinical and pathological picture as a whole has resulted in more confusion than clarity. The microscopical findings alone are not sufficient to distinguish between Hashimoto's and Riedel's struma, or between these and certain cases of exophthalmic goiter, myxedema, syphilis, tuberculosis, chronic inflammation, degeneration and fibrous replacement in and around adenomata, and involutional changes in senility.

In collecting data on the cases under consideration, specific information concerning age, sex, the previous existence of goiter; duration of symptoms; duration of the goiter; the extent as well as the character of the involvement of the thyroid; limitation of the process to the thyroid or extension beyond it (including more than the mere statement that the gland was adherent); adhesions to the trachea as opposed to adhesions to surrounding structures; the presence in the thyroid of adenomata, cysts, areas of calcification, frank inflammation, including small or large abscesses; the presence or absence of hyperthyroidism and hypothyroidism before and after operation; the amount of tissue removed; the character of the thyroid tissue remaining; the gross characteristics of the lesion, and finally the microscopical findings, will aid in satisfactorily orienting ourselves in regard to this problem.

The following conceptions concerning the nature of these two types of lesions have proved useful to us:

1. The group of cases generally classified as Riedel's disease, ligneous thyroiditis, productive thyroiditis (exclusive of specific infections, such as typhoid, tuberculosis, syphilis, actinomycosis, etc.) may be looked upon as having a local inflammatory process in the thyroid for which an etiological factor should be sought. In these cases the general body economy is affected only secondarily by reason of destruction of the thyroid, interference with respiration and deglutition, and injuries to important blood vessels and nerves. Such a process has its counterpart in other organs and tissues, and may be expected to behave in a similar manner, except for the fact that the thyroid gland is so situated that complications can occur readily.

2. The changes which occur in the thyroid in the presence of the Hashimoto type of lesion may be considered primarily to be local manifestations of a constitutional disorder, the nature of which is as yet not understood. What the initial changes in the thyroid may be is not known, but it seems clear that in the course of time these changes tend to become degenerative (rather than inflammatory) and sclerosing, and ultimately may be accompanied or complicated by more definitely inflammatory phenomena of a non-specific character. The lymphoid tissue, which is variable in amount and to a less degree in character, is non-specific for Hashimoto's struma.

3. The possibility of the transition from struma lymphomatosa (Hashimoto) to lymphosarcoma of the thyroid should be considered. A patient in whom this occurrence seemed probable came under observation and was operated upon in March, 1930. Further details of this case will be published later. Recently I had the opportunity of examining the clinical record and the sections from a similar and even more suggestive case sent to me by Dr. Lawrence W. Smith, of New York, to whom I am indebted for the privilege of mentioning the observation at this time. In view of these two cases, a review of lymphosarcomata of the thyroid in general, with due consideration of struma lymphomatosa as a possible point of departure, seems necessary but is beyond the scope of the present paper.

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SACRAL CHORDOMA

JAMES A. DICKSON AND C. A. LAMB

In the present paper, the writers offer another authentic case of chordoma to add to the rather meagre number now reported. A review of the literature has revealed accounts of only slightly more than eighty cases of all varieties. Most of these have been situated, as was this one, in the sacral area, the next most frequent site being the spheno-occipital region, although in the past few years some cases occurring along the spine at various levels have been reported. Probably, chordoma is not so rare as the number of reported cases indicates, many such tumors being either overlooked or incorrectly diagnosed.

History of the Case. This patient was a man aged forty-one, a manufacturer, who came to the clinic September 10, 1929, complaining of pain in the lower part of his back. This pain began in December, 1928. It was very mild at first, but increased slowly in intensity. It was of a constant boring character not affected by activity, and interfered with the patient's sleep. Heat, aspirin, and periods of rest had failed to give relief and after months of annoying and unrelievable pain in the lower spine, occasionally radiating down the left leg, a consultation was sought.

The findings on physical, laboratory, and x-ray examinations were negative, except for a tender area the size of a fifty-cent piece over the lower third of the sacrum exactly in the mid-line. This area could be definitely delimited, and neither pressure over the surrounding parts nor manipulation of the lumbosacral or sacro-iliac joints produced any pain. Rectal examination revealed a bulging area on the anterior surface of the sacrum in its lower third which was tender and semifluctuant. There was no fixation of the soft tissues, and the coccyx was free and movable and not painful.

Exploration, September 14, 1929, revealed a tumor mass, yellowish, soft, and very friable, which protruded from the posterior surface of the sacrum and extended through to its anterior surface, the area of bone erosion being about 2 centimetres in diameter. A portion of the tissue was removed for pathological study, and frozen sections were made at this time but were not sufficiently clear to permit of a diagnosis. The tumor was curetted out as thoroughly as possible, its bed was packed with vaseline gauze, and the wound was closed.

Our pathologist, Dr. Allen Graham, reported that macroscopically, the specimen consisted of numerous grayish-pink pieces of

tissue, soft, friable, and of a somewhat gelatinous consistency. Microscopically, the appearance of the tumor tissue was variable. There were areas in which small and large solid nests, strands, and masses of tumor cells were lying in a homogeneous pink-staining mucoid stroma. The tumor cells varied considerably in size and shape. In general, they were made up of a large amount of homogeneous, pink-staining cytoplasm, containing a relatively small,
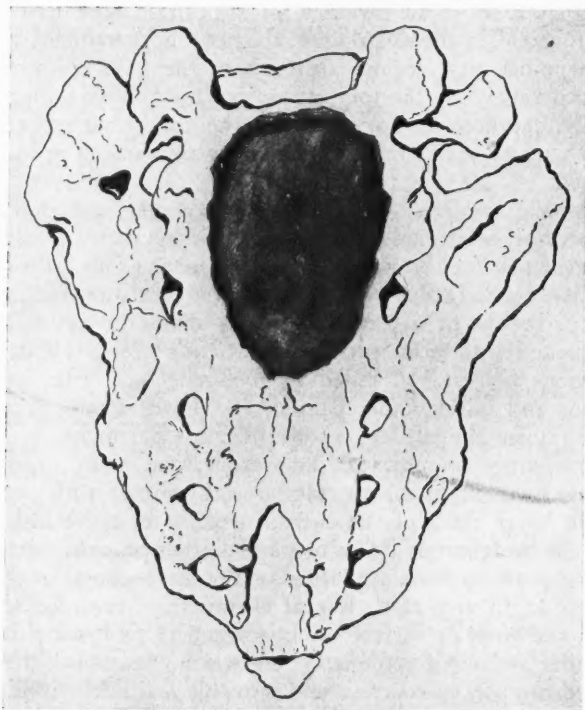
Fig. 1. Drawing of sacrum showing the relative size and position of the c h or doma at the time of the second operation.

round, spindle-shaped, or irregular nucleus. The nuclei were vesicular, and had well-defined nucleoli. The cell outlines were not distinct. There were large masses of multinucleated cytoplasm which had the appearance of syncytial tissue. The cytoplasm was vacuolated in many instances. In some areas the tissue was made up of compact masses of spindle cells, forming fibrillae and whorls, little of the mucoid stroma being present, and the picture was not unlike that

seen in a fibroma or fibrosacroma. The nuclei of the cells were variable in size and shape, and a few mitotic figures and irregular nuclear divisions were observed. In other areas there was a mixture of the two histological types described above. In a few areas the arrangement of the tissue was somewhat suggestive of cartilage.

The pathological diagnosis was *sacral chordoma*.

September 19, 1929, the sacrum was radiated with 900 r-units. The patient was discharged from the hospital September 22, 1929. He was free from pain, but there was a slight seropurulent discharge from the wound. Subsequently he reported regularly for dressings and observation until March 10, 1930. Although there had not been any return of discomfort nor any external evidence of a recurrence of the tumor up to this time, on rectal examination a mass was palpable which seemed to be slowly increasing in size. Another attempt at complete excision was therefore advised.

The second operation was performed March 27, 1930. Preoperative rectal examination revealed a sessile mass in the hollow of the sacrum, about the size of a silver dollar and approximately 8 millimetres thick. The centre of this mass felt softer than the surrounding portion.

The old scar over the sacrum was excised. Considerable scar tissue was found under the skin. The spines of the sacrum were exposed with the periosteal elevator, and the ligamentous structures were reflected. There was a small opening into the sacral canal of about 1½ by 3 centimetres. Through this could be seen a soft mass, bluish-gray in color. The roof of the sacrum was cut away by rongeurs, leaving an opening 5 by 10 centimetres in size. The whole of the sacral canal was filled with a fairly firm, bluish-gray tumor mass, which was remarkably avascular except at the periphery (Fig. 1). In the lateral portion of the mass, bundles of tissue could be seen which were identified as the sacral nerves. The tumor apparently filled the entire sacral canal, and was intimately associated with the sacral nerves. It was deemed inadvisable, therefore, to attempt to remove it because of the probability that these nerves would be injured. A rectal examination was made at this juncture, and pressure was applied to the anterior aspect of the tumor in the hollow of the sacrum. This mass could be seen and felt to bulge slightly just to the left of the mid-line at about the mid-portion of the sacrum. The patient made a satisfactory operative recovery and was discharged from the hospital April 6, 1930.

Post-operative treatment consisted of deep x-ray therapy in doses of 160 r-units on April 26, May 3, May 10, May 24, and
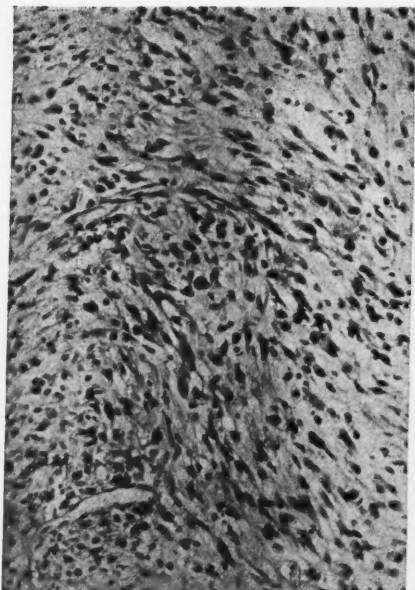
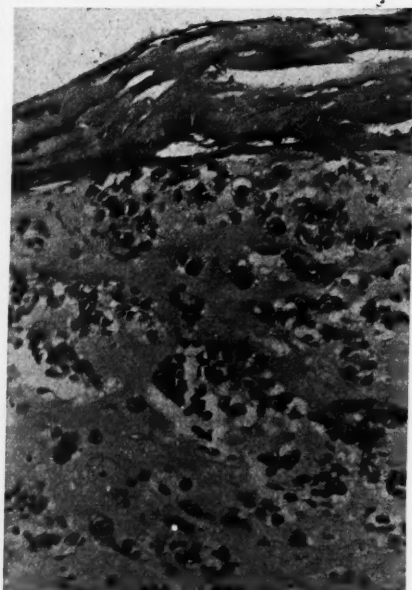Fig. 2. View of a section, X 150, showing the spindle-cell type of tissue.

Fig. 3. View of a section, X 150, showing the fibrous capsule of the tumor and the cartilage-like tissue with mucinous stroma.
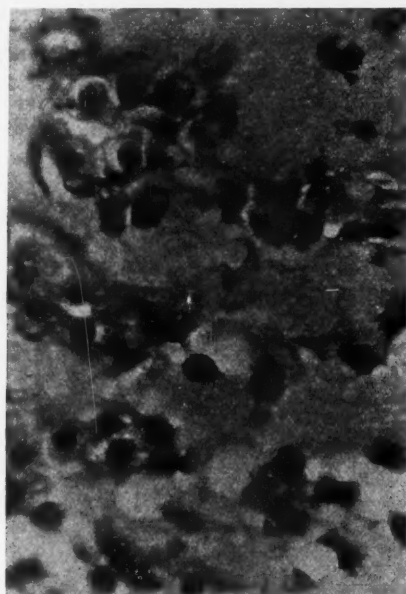
Fig. 4. View of a section, X 600, showing the syncytial-like masses of cells with vacuolated cytoplasm.

June 10, 1930. During this time the tumor progressively decreased in size and gradually became harder and more calcified.

When last examined, September 9, 1930, the patient had continued free from pain, and rectal examination revealed that the tumor was definitely smaller, while all tenderness had disappeared. The x-ray treatments apparently had been successful in checking the development of the neoplasm. Metastasis is rare in this type of tumor, and none has been found in this case.

Chordoma is a tumor arising from cellular remains of the notochord, occurring, therefore, along the spine, most frequently at its extremities. It is composed of epithelial tissue, and is of endothelial origin.

· As far back as 1856 Luschka described a case of chordoma, but did not recognize its origin or importance. Müller in 1858 suggested that the notochord was perhaps the origin of these tumors. The name "chordoma" was suggested by Ribbert in 1894. The development of our present knowledge has occurred almost entirely during the past thirty years, more particularly since 1922, when Professor Matthew J. Stewart, of Leeds, presented the first case recognized in Britain. In 1926 Professor Stewart collected fifty-seven reported cases, and in 1929 reports of only eighty cases had appeared in all the medical literature, and even some of these are questionable.

The average age at the onset of these tumors is from thirty-five to forty years, although cases have occurred as early as one and a half and as late as seventy-nine years. Spheno-occipital chordomas appear, on the average, ten years later than sacrococcygeal chordomas.

Males are twice as prone as females to develop these tumors, which suggests the part that trauma may play in their etiology. As a matter of fact they have been produced experimentally in rabbits by puncturing the body of a vertebra.

The first symptom noticed usually is mild pain in the sacrum or lower portion of the spine, located exactly in the mid-line. Pain may radiate down the legs or into any region upon the nerve supply of which the growth encroaches. Relief cannot be obtained by the ordinary therapeutic measures, and the pain gradually increases until sleep becomes almost impossible. While the tumor may be discovered before the occurrence of pain, more often it is found as a result of the pain. The mass may protrude principally within the bony pelvis, and thus escape detection unless the sacrum is palpated by rectum. Chordomas grow very slowly, but their persistence has been regarded as certain.

Usually there are no symptoms except those caused by mechanical pressure. The diagnosis is suggested by the history of pain in the lower spine or skull and by the finding of a palpable tumor mass, semifluctuant in character. A positive diagnosis, however, can be made only by the microscopic appearance.

In 1926, Stewart and Morin described the gross appearance of these tumors in detail. The growth is well encapsulated, rounded, and lobulated. Gross section appears lobulated, and the lobules show mucoid degeneration, often of an advanced character. Frequently, cells of syncytial type are embedded in a sea of mucin. Some areas resemble colloid carcinoma, others cellular carcinoma. The salient microscopic features described by Stewart are as follows: aveolar character of growth; solid epithelial aspect of the younger cellular areas; cytoplasmic and intercellular vacuolation; formation intracellularly of mucinous fluid, which escapes from the cells to form, first, intercellular columns and, later, mucin in which only scattered cellular islets remain; rarity of mitotic figures except in very malignant cases. Chordomas are malignant only in a low degree, but occasionally they metastasize.

Although in the great majority of cases reported so far radiation has not helped, from the results in this case it is our opinion that the x-ray, in sufficient dosage, has greater possibilities than surgery. The end-result of our case, of course, is uncertain, but the improvement thus far has been satisfactory. The size of the tumor has decreased, the tissues have hardened, and all symptoms have disappeared.

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W. C. ROENTGEN AND THE DISCOVERY OF THE ROENTGEN RAYS

Otto Glasser

Thirty-five years ago, on November 8, 1895, Wilhelm Conrad Roentgen made the revolutionary discovery of a mysterious new kind of ray which he called the "x-ray." Thirty-five years is too short a period of time in which to obtain the proper perspective by which to judge the significance of this revelation or to appreciate fully the genius of the man who made this remarkable discovery and beneficently gave it to the world. On the other hand, thirty-five years is so long ago that it is difficult to obtain authentic facts from original sources bearing directly upon the manner in which the existence of the roentgen rays was first revealed to their discoverer. Fortunately, however, there are some persons still living who had personal and intimate contact with Roentgen and can relate their experiences with authority, and who can also vouch for the veracity of the early reports of the discovery.

According to the statements made by these persons, this peculiar and inexplainable phenomenon was first manifested by the fluorescence of a small barium platinum cyanide screen under the influence of the penetrating rays emitted from an excited Crookes tube. A detailed description of Roentgen's discovery was given by Sylvanus P. Thompson, a well-known English physicist, himself an enthusiastic x-ray research worker and president of the newly founded British Roentgen Society, at a meeting held on Friday, November 5, 1897, at St. Martin's Town Hall in London. Roentgen had modestly declined an invitation to address this historic meeting. Thompson's report of the discovery agrees with many others, and according to our studies, must have related the events as they actually occurred. Sylvanus P. Thompson said in this address:

"November the eighth, 1895, will ever be memorable in the history of Science. On that day a light which, so far as human observation goes, never was on land or sea, was first observed. The observer, Prof. Wilhelm Conrad Roentgen. The place, the Institute of Physics in the University of Wurzburg in Bavaria. What he saw with his own eyes, a faint flickering greenish illumination upon a bit of cardboard, painted over with a fluorescent chemical preparation. Upon the faintly luminous surface a line of dark shadow. All this in a carefully darkened room, from which every known kind of ray had been scrupulously excluded. In that room a Crookes' tube,

stimulated internally by sparks from an induction coil, but carefully covered by a shield of black cardboard, impervious to every known kind of light, even the most intense. Yet in the darkness, expressly arranged so as to allow the eye to watch for luminous phenomena, nothing visible until the hitherto unrecognized rays, emanating from the Crookes' tube and penetrating the cardboard shield, fell upon the luminescent screen, thus revealing their existence and making darkness visible.

"From seeing the illumination by the invisible rays of a fluorescent screen, and the line of shadow across it, the work of tracing back that shadow to the object which caused it, and of verifying the source of the rays to be the Crookes tube, was to the practiced investigator but the work of a few minutes. The invisible rays — for they were invisible save when they fell upon the chemically painted screen — were found to have a penetrative power hitherto unimagined. They penetrated cardboard, wood, and cloth with ease. They would even go through a thick plank, or a book of 2000 pages, lighting up the screen placed on the other side. But metals such as copper, iron, lead, silver and gold were less penetrable, the densest of them being practically opaque. Strangest of all, while flesh was very transparent, bones were fairly opaque. And so the discoverer, interposing his hand between the source of the rays and his bit of luminescent cardboard, *saw* the bones of his living hand projected in silhouette upon the screen. The great discovery was made."

This report, given here in the exact words of the great English scientist, was published in November, 1897, in the second volume of the world's first journal of roentgenology the English *Archives of Skiagraphy*, or as it was afterwards called, the *Archives of the Roentgen Ray*.

Inevitably many stories and fables are spun about discoveries and inventions of great significance and the birth of the x-ray did not escape this fate. The most popular story, perhaps, is the myth of the book and the key. It is repeated from time to time and recently again made the rounds through the newspapers in the following form:

"Prof. Roentgen once placed an experimental electric tube upon a book beneath which was a photographic plate holder, loaded. Some time later he used the plate in his camera and was puzzled, upon developing it, to find the outline of a key on the plate. He investigated and discovered a key between the pages of the book on which the experimental lamp had rested. The strange 'light' from the electrical discharge in the glass tube had penetrated the covers

and pages of the book and the shield of the plate holder. Thus the x-ray was discovered."

I have found this story to be unknown outside of the United States, and it certainly did not originate in Germany, but it is one which appeals to the imagination of the general public. It seems to be traceable to an account of a Chicago scientist by the name of T. S. Middleton who in 1895 was a student at the Wurzburg University and who incorrectly placed the date of the discovery in the Spring of the year 1895.

This story contains some inaccuracies even in its original form. The incident might have taken place after the discovery of the rays and if it did occur it might have directed Roentgen to the study of the photographic effect of the rays, but there are many reasons for questioning the veracity of this tale. Roentgen never spoke of any observations which might have had anything whatever to do with such an experiment. If this observation had been made in April, 1895, Roentgen would certainly have been the first to refer to it because he was always most conscientious and accurate in recording his data. Even Roentgen's two assistants, one of whom helped him to operate the vacuum pump with which the Hittorf and Crookes tubes were evacuated, did not know about the discovery of the x-ray until it was publicly announced late in December. If these co-workers who were in rather intimate touch with Roentgen's work did not know about the discovery until it was announced publicly, how much less insight must the students at the University have had into the work of their Professor! One of the few persons who knew about the discovery before the announcement was made was Roentgen's wife, Bertha. One evening in November, 1895, she became very angry with her absent-minded husband because he did not comment upon the excellent dinner she had prepared for him, and he did not even notice that she was angry until she asked him what was the matter. He finally took her downstairs to his laboratory, which was in the same building, and for the first time presented to her astonished eyes the wonders of the x-ray. We have in our museum a letter which Mrs. Roentgen wrote in March, 1896, to Prof. Roentgen's cousin, Mrs. L. R. Grauel, of Indianapolis, in which she relates how her husband told her of the discovery for the first time in November, 1895. This statement is, therefore, of great significance as it fixes the date of the discovery.

Another fable connected with the discovery, which occasionally emerges from oblivion and which was even recently broadcast by radio from Hamburg, is the story that the first observation of the fluorescent light was made by Roentgen's laboratory servant. It is

Fig. 1. Photograph of Wilhelm Conrad Roentgen taken at the time of his discovery of the x-rays. (From "Les Prix Nobel en 1901," Norstedt, Stockholm, 1904.)

perhaps of psychological interest that envious or ignorant individuals often repeat such stories in spite of well-founded historical facts to the contrary.

Roentgen's adopted daughter, who now lives in Hanover, Germany, but who at the time of the discovery was living with her foster parents in the Wurzburg Institute, states in a letter of April 2, 1930, that she remembers very distinctly that on the evening in which her father discovered the rays he was alone in his laboratory. Roentgen himself wrote a letter to Mrs. Boveri on April 28, 1921, in which he says in his characteristic manner: "Do you know that now Zehnder also heard the story that I did not make the first observation of the effects of the x-rays, but that an assistant or servant discovered them. What miserable envious man has invented this story?"

Was Roentgen's discovery of the roentgen rays accidental? Popular opinion would have us believe that it was! However, a careful study of the personality and the scientific background of Roentgen himself, as well as the events which led up to the actual discovery, and of the published comments of contemporary scientists, should emphatically disprove this theory. Roentgen was undoubtedly one of the outstanding physicists of the nineteenth century, even without taking into consideration his discovery of the roentgen rays. He began to experiment with cathode rays in October, 1896, because he was interested in many riddles which still existed in spite of valuable contributions to the subject which had been made by other investigators. Like all research scientists he was on the lookout for new phenomena, and was following in the path of all his illustrious predecessors from von Guericke to Lenard when he discovered "a new kind of ray." Roentgen's discovery was the final step in a brilliant and logical correlation of a multitude of facts which had been disclosed by many scientists. His glance at the fluorescent screen may be said to be the only accidental incident connected with the discovery. But how well Roentgen knew the explanation of this almost insignificant phenomenon! Many scientists before him — Crookes, Goodspeed, Goldstein, Lenard, and others — had made similar observations but had entirely forgotten about them until Roentgen's announcement was made. It was his keen observation and the accuracy of his critical judgment, together with his great experimental skill which made his discovery of such tremendous significance.

It is interesting to note that one year before Roentgen made his discovery he gave an address as the President of the Wurzburg University and in this speech quoted some of the thoughts of one of his

predecessors in the chair of Physics and Philosophy, Prof. P. A. Kircher, who as early as 1602 made the following statement: "Nature often reveals the most astonishing phenomena by the simplest means, but these phenomena can only be recognized by persons who have sharp judgment and the investigative spirit, and who have learned to obtain information from experience, the teacher of all things." How applicable this centuries-old assertion

Fig. 2. First x-ray picture of a hand taken by Roentgen in November, 1895. (Courtesy of the Physical-Chemical Institute of the University of Vienna, Prof. Dr. E. Haschek.)

was destined to become in the case of Roentgen's own discovery and how strange that he should have quoted it a year before the great event! Very similar in spirit was that short comment which was made by the philosopher, Münsterberg, of Harvard University, shortly after the announcement of the discovery when he refused to subscribe to the idea that it was entirely accidental by saying, "Suppose chance helped, there were many galvanic effects in the world before Galvani saw by chance the contraction of a frog's leg

on an iron gate. The world is always full of such chances, and only the Galvanis and Roentgens are few."

After the first observation of the fluorescent effects of the unknown rays, Roentgen feverishly followed the clue and in the next few weeks performed an astonishing number of carefully planned experiments. We know from his wife's story that Roentgen seldom emerged from his laboratory during these weeks, that he had his meals there, and that he even slept there part of the time in order to be undisturbed and to be ready day or night to try out any new ideas that might come to him in the course of his work. Such new ideas certainly must have been numerous. Today it is difficult to imagine the multitude of unknown and complicated phenomena with which the scientist had to wrestle during those first days. The replacing of the fluorescent screen by the recording photographic plate was one of his first important successful steps. Many of his first pictures which show the varying absorbability of many materials were produced in this way. His first roentgenograms of the hand of his wife (Fig. 2), a compass, metal weights in a wooden box, and so forth, have come to have historic significance. At first the photographic plate became more popular as a method of demonstrating the effects of the new rays, and for a time this method overshadowed the use of the fluorescent screen to such a degree that the latter almost faded into oblivion, reappearing, however, many months later under the name of the Edison Fluoroscope, Salvioni cryptoscope, and so forth, when it was hailed enthusiastically as another new discovery which made the rays visible to the eye. It seems that the significance of this supposed improvement almost eclipsed that of the discovery of the rays. Essentially, however, these improvements were only slight modifications of Roentgen's original experiment.

By means of his screen and plates Roentgen made all of the fundamental observations which he reported in his first two classical communications with such accuracy and thoroughness that other physicists and investigators could add nothing new to the master's original work until many years later. Roentgen showed the propagation of the rays in straight lines. He observed that they were not reflected or refracted or deviated by the influence of magnetic fields. He investigated the penetration of the rays through different materials which are entirely opaque to ordinary light. He made observations on the hardening of the rays by absorption, the creation of secondary radiation and the conductivity of air when traversed by the rays, and recorded many other properties.

On December 28, 1895, Roentgen handed his "preliminary" com-
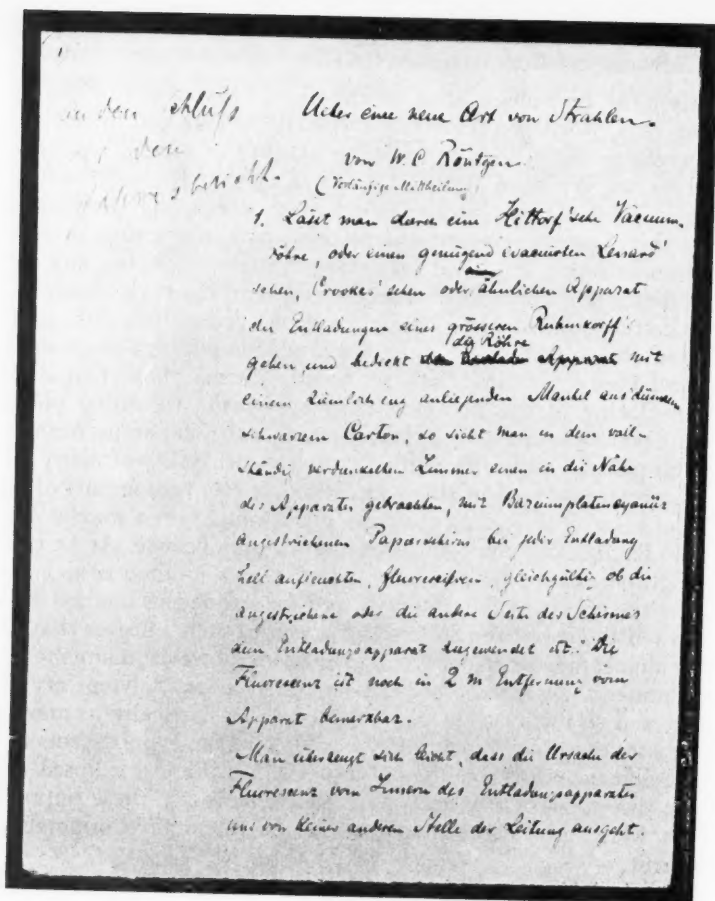
Fig. 3. Original manuscript of Roentgen's first paper "On a New Kind of Ray." (Courtesy of the Physical Institute of the University of Wurzburg, Director, Prof. Dr. Harms.)

munication, "On a New Kind of Ray," to the President of the Wurzburg Physical Medical Society (Fig. 3). It was accepted for publication in the Annals of the Society for the year 1895, although he had not yet lectured on the subject. No meetings or lectures are given in German universities during the Christmas vacation, therefore Roentgen waited until the 23rd of January, 1896, before he spoke publicly on the subject of his discovery for the first and apparently the only time.

During this month the news of the discovery travelled with almost unbelievable rapidity from the quiet laboratory of the sleepy little town on the river Main to the four corners of the world. The public press in the capitals of Europe and America printed the news even before the Wurzburg newspaper, the *General Anzeiger*, printed its first report. This sudden world-wide publicity was not entirely to the liking of the modest discoverer, and the earliest reports went to press without his consent. He had sent some of his first x-ray pictures to a few friends, before the news of the discovery was published. One of these was Prof. F. Exner, in Vienna, who had been a friend of Roentgen since their college days in Zurich. One evening Exner showed the pictures to a little gathering of fellow scientists. They naturally created quite a sensation and some heated comments were made. Prof. Ernst Lecher, of Prague, asked Exner to let him have the prints until the next morning. Late at night Lecher hastened to bring the good news to his father, Z. K. Lecher, who was then the publisher of the *Wiener Presse*. Even in those days newspaper men had their uncanny sense for news, and the next morning edition of the *Presse* contained an elaborate article on the revolutionary discovery by the "Wurzburg Professor." The news was quickly copied by other continental papers and on the evening of January 6, 1896, it was cabled from London to all of the civilized countries of the world in the following words: "The noise of war's alarm should not distract attention from the marvellous triumph of science which is reported from Vienna. It is announced that Prof. Routgen of the Wurzburg University has discovered a light which for the purposes of photography will penetrate wood, cloth and most other organic substances." A more detailed report of the discovery followed the next morning, and in a few days the almost unbelievable story of the "all-penetrating rays" had found its way not only into the newspapers but also into the scientific journals.

The *Electrical Engineer, New York,* reported the discovery on January 8, 1896 (Vol. 21, p. 51), under the title, "Electrical Photography through Solid Matter;" the *Electrician, London,* followed with an article on January 10, 1896 (Vol. 36, p. 334), under the headline "Sensational Worded Story." A detailed article also appeared in the January number of the Italian *Il nuovo cimento,* while the French *L'eclairage electrique* published its first comments on the discovery on February 6, 1896. The London *Nature,* and the New York *Science* had somewhat more elaborate articles in their issues of the 16th and 25th of January.

Although at first it appeared as if the technical journals would claim the discovery, the valuable medical possibilities of the use of

the x-ray for diagnostic purposes immediately became apparent and the *Münchener medizinische Wochenschrift* of January 14, 1896, reported a meeting of the Berlin Society of Internal Medicine, which took place on January 6, 1896, at which the neurologist, Dr. Jastrowitz, spoke on Roentgen's discovery. Further comments appeared in the same journal the following week. On January 16 the *Wiener klinische Wochenschrift* (Vol. 96, p. 48), reported Prof. S. Exner's talk on the x-ray. The English *Lancet* and also the *British Medical Journal* contained the first news in their issue of January 11 under the title, "The Searchlight of Photography;" the French *Comptes rendus* of January 20, and the Italian *La settimana medica* of January 25, under the title "Experiences with the Roentgen Light," *Medical Record*, New York, January 11, 1896, under the title "Illuminated Tissues," and the *Journal of the American Medical Association* on February 15, 1896. These early communications show the alacrity with which the medical profession accepted the new weapon and promptly used it to good advantage, at the same time anticipating the vast possibilities of improving diagnosis by improving the new tool. Even the fondest hopes of those first days following the discovery were soon surpassed in the romantic development of roentgenology.

Roentgen's name and the news of his discovery thus became known throughout the whole world, and much progress had already been made even before the modest discoverer spoke for the first and only time on his "New Kind of Ray." The lecture was given before the Physical Medical Society of the University of Wurzburg on January 23, 1896, in the auditorium of Roentgen's Physical Institute. Long before the meeting began every seat of the large room was occupied. Professors of the University, high officials of the city, representatives of the Army, and many students, filled the room. With great excitement and enthusiasm the crowd was waiting for the discoverer, and when he entered a veritable storm of applause arose which was repeated many times during the evening. Roentgen modestly expressed his thanks and just as modestly began to talk about his work. He emphasized first that on account of the general interest he thought it his duty to speak publicly about his "Arbeit," although the experiments were still in the course of development. He then mentioned the investigations with cathode rays made by Hertz, Lenard, and others, and said that his own observations had led him to make experiments along the same lines which resulted in his discovery. He related how he first observed the fluorescence of a small piece of paper painted with barium platinum cyanide and how he quickly found out that the cause for

this fluorescence came from the carefully covered Hittorf tube itself, and not from any other part of the high tension circuit. "I found by accident," the discoverer said, "that the rays penetrated black paper. I then used wood, paper, books, but I still believed I was the victim of deception. Then I used photography and the experiment was successful."

Roentgen demonstrated numerous successful experiments with the x-rays and also mentioned his well-known earlier attempts to make photographs through a door in his laboratory with the result that he found light strips on the exposed plate which were unexplainable. Upon dismantling the door he found that the strips of white lead which held the panels of the door together were responsible for the increased absorption of the rays and caused the light strips on the plate. He then exhibited various x-ray pictures and they, of course, excited the greatest interest. After the demonstration Roentgen asked the famous anatomist of the University, His Excellency von Kölliker, to permit him to photograph his hand (Fig. 4). Von Kölliker eagerly complied with this request and when the excellent picture was shown a little later there was tremendous applause and all present felt that this was a moment of real historical significance. Von Kölliker said feelingly that in his forty-eight years of membership in the Physical Medical Society he had never attended a meeting at which a subject of such great significance had been presented. He finished with three cheers for the discoverer and proposed that henceforth the x-rays be called roentgen rays. This suggestion was adopted amid renewed applause for Roentgen. The general optimism was again expressed in a short discussion and only one of those present, the surgeon, Prof. Schoenborn, warned against too much optimism since the method hardly promised to be of much if any value in diagnosing internal disturbances.

Prof. Lehman, who was then President of the Physical Medical Society and now is Professor of Hygiene at the Wurzburg University, has related part of the story given above and substantiated some of the early reports of this meeting which appeared in various journals. He stated recently that many of those present at the meeting met afterwards and had a glass of beer, and that they looked with keen optimism into the future, but "whatever our dreams then expected, they have been far surpassed by the actual facts."

From then on a veritable flood of articles on the new "wonder rays" appeared in rapid succession in the press of the whole world. I have been able to collect over a thousand articles on x-rays which appeared in scientific journals during the year 1896. Over fifty books on the same subject were published in the same year, not to mention

the innumerable comments which appeared in some of the popular and semi-scientific journals.

The cartoons and poems appearing in many popular magazines and newspapers form a most interesting part of the early printed records of the discovery and give us a good idea of its reception by the general public (Fig. 5). Not infrequently they express a certain

Fig. 4. Roentgenogram of von Kölliker's hand, taken by Roentgen after his first lecture on the x-ray on January 23, 1896.

fear of the ghastly skeletal pictures which was voiced also in many publications. As an example we may quote from the London *Pall Mall Gazette:*

"We are sick of the roentgen rays. It is now said, we hope untruly, that Mr. Edison has discovered a substance — tungstate of calcium is its repulsive name — which is potential, whatever that means, to the said rays. The consequence of which appears to be that you can see other people's bones with the naked eye, and also

[JANUARY 25, 1896.]   PUNCH,

THE NEW PHOTOGRAPHIC DISCOVERY.

THANKS TO THE DISCOVERY OF PROFESSOR ROENTGEN, THE GERMAN EMPEROR WILL NOW BE ABLE TO OBTAIN AN EXACT PHOTOGRAPH OF A "BACKBONE" OF UNSUSPECTED SIZE AND STRENGTH !

THE NEW ROENTGEN PHOTOGRAPHY.
"LOOK PLEASANT, PLEASE."

Fig. 5. Two early cartoons of Roentgen's discovery of a "New Photography." (From "*Punch*" and "*Life*.")

see through eight inches of solid wood. On the revolting indecency of this there is no need to dwell. But what we seriously put before the attention of the Government is that the moment tungstate of calcium comes into anything like general use, it will call for legislative restriction of the severest kind. Perhaps the best thing would be for all civilized nations to combine to burn all works on the roentgen rays, to execute all the discoverers, and to corner all the tungstate in the world and whelm it in the middle of the ocean. Let the fish contemplate each other's bones if they like, but not us.'"

This same ignorance and pessimism found expression in jokes and poems as well as in everyday life. On February 19, Assemblyman Reed, of Somerset County, New Jersey, introduced a bill into the House at Trenton, New Jersey, prohibiting the use of x-rays in opera glasses at theaters,[2] and in London, England, a firm "made prey of the ignorant women by advertising the sale of x-ray proof underclothing.[3]" Numerous poems were published, one of which reads:

> O Roentgen, then the news is true
> And not a trick of idle rumor,
> That bids us each beware of you
> And of your grim and graveyard humor.

89

We do not want, like Dr. Swift,
To take our flesh off and to pose in
Our bones, or show each little rift
And joint for you to poke your nose in.

We only crave to contemplate
Each other's usual full dress photo
Your worse than "Alltogether" state
Of portraiture we bar in toto!

The fondest swain would scarcely prize
A picture of his lady's framework;
To gaze on this with yearning eyes
Would probably be voted tame work.

No, keep them for your epitaph,
These tombstone souvenirs unpleasant;
Or go away and photograph
Mahatmas, spooks and Mrs. Besant.*
    — *From London "Punch," Jan. 25, 1896.*

*In this connection, it is interesting that a recent number of *Time* (February 9, 1931) contained a review of a biography just published of Mrs. Besant —"The Passionate Pilgrim" by Gertrude Marvin Williams. The first paragraph of this review is as follows: "Annie Wood Besant (rhymes with either incessant or pleasant) is an old woman (83) popularly associated with occult ritual and mystic robes. She is still president of the Theosophical Society, but perhaps you didn't realize she was once a parson's wife, an atheist, a Socialist, a beautiful spellbinder." And the review concludes: "At present she is a still energetic old woman who stands as temporal Head to some 43,000 scattered Theosophists."— ED.

However, this scattered opposition could by no means stop the triumphal course of events. The hopeful individuals by far outnumbered the fearful ones, some of them even believing that with the new knowledge all the age-old problems of spiritualism, soul photography, vivisection, temperance movements, Philosopher's stone would be solved. The New York newspapers actually reported that at the College of Physicians and Surgeons the roentgen rays were used to reflect anatomical diagrams directly into the brains of the students, making a much more enduring impression than the ordinary methods of learning anatomical details.[4]

A romantic chapter in the history of science is the story of the feverish activities which were in progress in laboratories all over the world during the first weeks following Roentgen's great discovery. Many prior claims were made and many attempts were made to find a better name for the new phenomenon. In rapid succession

came suggestions for technique and for practical uses for the rays in medicine, and efforts were made to solve the secret of the essential character of these rays. First obser vations of the physiological effects of the rays, especially on the human skin, were soon reported. It would lead much too far, however, to discuss at this time all the fascinating phases of Roentgen's discovery. They have been dealt with in detail in my book.[5]

Very quickly Roentgen's work received proper recognition. Emperor Wilhelm invited him to Potsdam to give a demonstration of his discovery and conferred a decoration upon him. The Prince Regent of Bavaria, Luitpold, bestowed upon him the "Verdienst Orden" of the Bavarian crown with which the coveted "von," the sign of nobility was connected. Roentgen declined to accept this latter honor. His University gave him an honorary degree of M.D., and his birthplace, Lennep, made him an honorary citizen. Italy decorated him with the Order of the Italian Crown, and England gave him the Rumford Medal. He was honored by the whole world as hardly any scientist had been before, but still he remained a modest, industrious man. In spite of all the excitement about him he continued his work after his first publication was printed, and as early as March, 1896, he was ready to give his second communication to the press, this being an important addition to his first paper.

Mrs. Roentgen gives us a good insight into the strenuous life which Roentgen led during this time in the letter to her cousin which we mentioned earlier in this paper. She wrote on March 6, 1896:

"It is not easy to be a famous man, and very few people have any conception of how much work and how much excitement it carries with it. Our quiet home life was gone as soon as my husband had published his paper. Every day I must admire anew his enormous capacity for work and how he keeps his thoughts together in spite of the thousand and one small things with which he is annoyed. It is however high time now that he should take a rest and I am preparing everything for a few weeks' trip to the south where he can spend some time in the open. We are of course grateful that we are privileged to enjoy these wonderful times. How much recognition my husband gets for his untiring researches! Sometimes it would seem that all the praise and honors would make a person dizzy. It would be serious indeed if the man thus honored were conceited. You know my good husband very well and you surely can realize that his greatest recompensation lies in the fact that he could find something valuable in the field of pure science."

A few days after this letter was written Roentgen and his wife started on their trip south. They spent several restful weeks in beautiful Sorrento near Naples, where they stayed at the Hotel Victoria, and there Roentgen found his well-deserved rest. While he was in Italy he saw a note in the papers to the effect that "Prof. Roentgen the famous discoverer of the Roentgen rays was in Italy

Fig. 6. Photograph of Roentgen as a young student.

and had been seen in Rome in a dark brown suit." He immediately packed that brown suit at the bottom of his trunk because he was very shy, and did not want to be famous. He always tried to avoid publicity.

Upon his return from his vacation he continued to work on the x-rays throughout the year. The results of his investigations were published on March 10, 1897, under the title: "Further Observations on the Properties of the X-rays." This work rounded out his fundamental series of experiments on the x-rays.

After the news of Roentgen's discovery had been published, the general public wanted to know more about the man who was successful in opening the door to new wonderlands of science. Naturally the first newspaper accounts of Roentgen himself were rather meager. His name was misspelled "Routgen" through an error in transcription and was reprinted incorrectly in most of the early reports. He was said to be an Austrian professor and the place of the discovery was given as Vienna; this error was probably due to the fact that the first published news of the discovery came from Vienna, as has been previously explained. Soon, however, the clever reporters were able to find out more about his personal affairs and presented their readers with rather good biographies of the great scientist.

Wilhelm Conrad Roentgen was born on March 27, 1845,in Lennep, a little town on the Lower Rhine, in the heart of the industrial section of that part of Germany. His father, Friedrich Conrad Roentgen, a manufacturer and cloth merchant, had also been born in Lennop on January 11, 1801. The Roentgens came from an old Rhenish merchant family which can be traced back to the seventeenth century. Roentgen's mother, Charlotte Constance Frowein, was born in Amsterdam on February 25, 1806. She came from a Dutch family well known in industrial and shipping circles. Her father also was born in Lennep. Two of Roentgen's grandparents were cousins. Mrs. Roentgen's mother, Sussanna Marie Moyet, had also been born in Amsterdam. Her family originally came from Italy and emigrated to Holland in the seventeenth century.

Wilhelm Roentgen was an only child although his father and his grandfathers came from families of many children. Young Roentgen grew up in very happy surroundings. His mother had brought beautiful furniture, pictures, and china from Holland to their Lennep home and the boy early acquired a taste for art and beauty which he never lost throughout his life. Part of his childhood was spent in Holland with his mother's relatives in Utrecht and Apeldoorn. Later the Roentgens moved to Apeldoorn and their son attended the schools in Utrecht. He was not a particularly brilliant student, always preferring a hike through the fields and woods to dull and uninteresting lessons at school. His happy school days were suddenly interrupted. After a harmless student prank he was found to be guilty and since he did not wish to divulge the names of his accomplices he was expelled from the school. This was a severe blow to his ambitions. However, a great consolation in those dark days was the complete understanding of his beloved mother. He entered the school for machinists in Apeldoorn in order to prepare himself for the profession of his father. A little later he tried again

Fig. 7. W. C. Roentgen with his parents and other relatives. (Courtesy of the Physical Institute of the University of Wurzburg, Director Prof. Dr. Harms.)

to pass the examinations which would have given him the same credits as would graduation from the Utrecht school, that is, the right to enter college, but he failed and again had to return to the Apeldoorn school. It is doubtful whether these repeated attempts of fate to bar Roentgen from the regular scholastic courses were really a disadvantage. It would seem that freedom from the strict and often dry scholastic burden permitted the budding genius to develop along lines that later bore the finest of fruit. As often happens a happy coincidence threw new light into the darkness of young Roentgen's student experiences. A Swiss friend of the Roentgens, by the name of Thormann, told the young student that the Zurich Technical High School accepted students for matriculation without the usual credentials. So in the Spring of 1865 we find Roentgen in the beautiful city on blue Lake Zurich and on the road which led him to the highest peak of academic honors. The

well known Clausius, Professor of Theoretical Physics, and Kundt, the experimental physicist, awakened such a love for the physical sciences in the heart of the young student that he soon devoted himself entirely to this subject. His brillant career subsequent to this time is so well known that we will only cite a few of the important incidents of his life.

On June 22, 1869, he was graduated as Doctor of Philosophy and remained as assistant to his teacher, Kundt. Two years later he followed Kundt to Wurzburg where the former had accepted the offer of the chair of physics. In Wurzburg the two were forced to work under rather unfavorable circumstances in a poorly equipped "physical cabinet." While in Wurzburg, Roentgen married (on July 7, 1872) Bertha Ludwig, of Zurich, with whom he lived very happily for nearly fifty years. The Roentgens had no children but later adopted and raised a young niece of Mrs. Roentgen.

Once more a dark cloud crossed Roentgen's path. Since he had not the required credentials from Utrecht, the strict old traditions of the Wurzburg University would not permit him to become "Privatdozent" and thus to reach the first step of his academic career. However, at that time Kundt was called to the newly-founded German University in Strassburg and Roentgen went with him. Here in the newly-acquired Provinces was an atmosphere free from hampering traditions and after a short time (on March 13, 1874) Roentgen became Privatdozent of Physics at the Strassburg University. A year later (April 1, 1875) he was offered the chair of physics and mathematics at the Academy of Hohenheim which he accepted. However, as he was accustomed to the rather large and well-equipped laboratories of the University at Strassburg he did not feel very happy in the poorly equipped institute at the Hohenheim Academy. At Kundt's request he returned to Strassburg a year later and accepted the Associate Professorship of Theoretical Physics. Alone and also in collaboration with his teacher he published a series of excellent treatises on the merit of which he was offered the chair of physics at the Giessen University. He accepted this appointment on April 10, 1879, and stayed for almost ten years in the old Hessian city. Many of his most valuable researches were carried on in Giessen and here he spent some of his happiest hours and made some of his best friends. In later years he often recalled his pleasant trips from Giessen to the Rhine at the season of the wine festivals.

In 1888 Roentgen was called to the University of Wurzburg, the institution which a few years previously had refused to give him his academic standing. Here he succeeded the brilliant Kohlrausch

who had gone to Strassburg. It was in Wurzburg that he made the discovery of the x-rays in November, 1895.

We have already spoken of the many honors and compliments which were showered upon Roentgen after his discovery. Various institutes made efforts to obtain his services but he stayed in Wurzburg until April 1, 1900, when he accepted the call of the University of Munich and moved to the Bavarian capital by special request of the Bavarian government. In 1901 he was awarded the first Nobel prize. The years in Munich were filled with successful work and happy vacations. When the world war broke out times changed and Roentgen, who always loved his Fatherland, suffered from the hardships of the great conflict. In his loyalty he gave his gold and some of his valuable honorary medals to the government. The tragic results of the war weighed very heavily upon him and his hopes that the broken morale of the German people could ever be regained were almost gone. His beloved wife died on October 31, 1919, after a long illness and Roentgen was a very lonely and unhappy man. He died in Munich on February 20, 1923, of carcinoma of the intestines at the age of seventy-eight years, and his ashes were laid to rest in Giessen. His name and his work will live forever.

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A CASE OF TRAUMATIC RETROBULBAR ARTERIOVENOUS ANEURYSM

W. James Gardner *and* W. B. Hamby

The patient, a woman 32 years of age, entered the Clinic April 17, 1931, complaining of blindness in the right eye, protusion of the eye, and a constant swishing roar in the head synchronous with the pulse. On February 6, 1931, she had received a severe blow on the right supraorbital area in an automobile accident, the lacerations caused by this requiring suture. She immediately became unconscious and remained so for six days. On regaining consciousness she was blind in the right eye and a roaring noise was heard, which had been present constantly ever since. Hearing was diminished on the right side, and the patient was dizzy.

Examination revealed a right pulsating exophthalmos with a systolic bruit and blindness, palsy of the sixth nerve on the right side, irregular pupils, the right being larger than the left. The left pupil reacted to light and accommodation normally, the right consensually only. The palpebral fissures measured 11 mm. on the right, 8 mm. on the left. Dr. Ruedemann reported for the right eye: Convergence, marked conjunctival inflammation, pupil dilated to 5 mm., tortuosity of the ocular vessels, some edema. Disc shows definite atrophic change, the arteries and veins are approximately equal in size with some tortuosity of the vessels; definite macular hyperemia. Left eye: pupil 3 mm., disc normal.

Romberg's sign was positive, the patient falling to the right.

Lumbar puncture showed an initial pressure of 110 mm. water, a normal response to Queckenstedt's test, clear and colorless fluid. The spinal fluid showed a very faint trace of globulin, colloidal gold curve 5-5-5-5-5-2-1-0-0-0, Wassermann and Kahn tests 4 plus, total protein 30 mg. per 100 c.c. of fluid.

A roentgenogram of the right orbit showed erosion of the superior inner margin of the orbit. Other laboratory tests gave normal findings.

The patient was started on anti-luetic treatment. It was found that digital compression of the right common carotid artery against the carotid tubercle made the patient dizzy and weak after from two to three minutes. It also stopped the roar in her head and stopped the pulsation of the exophthalmos. To accustom her to diminished blood supply through the cerebral arterial system, we applied compression to the artery several times daily until on May 14th she could tolerate compression for twenty-five minutes with

ease. This was twenty-five days after the patient entered the hospital.

Operation — On May 15, 1931, the patient was operated upon. The head was rotated to the left, and under local anesthesia a
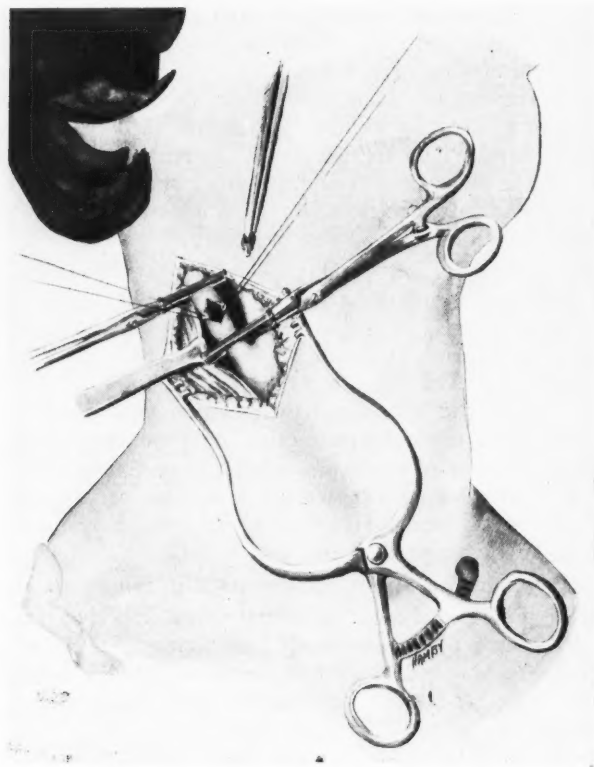

Fig. 1. An insertion of muscle plug into internal carotid artery

three-inch incision was made just anterior to the anterior border of the sternomastoid muscle on a level with the thyroid cartilage. The common carotid artery with its bifurcation was exposed. Compression of the external carotid did not affect the bruit, while compression of the internal carotid stopped it completely. The internal carotid was then dissected free for a distance of four cm. and

was clamped with two rubber-shod artery clamps. A vertical incision about 1 centimeter long was made into the lumen of the artery between the clamps. A purse-string suture of silk was placed around the incision, after which a piece of muscle from the platysma

Fig. 2-A

Fig. 2-B
Fig. 2. Roentgenograms of skull showing clip in place
(A) Anterior view
(B) Lateral view

was removed, cut to the size of a pea and clamped with a small silver clip. This was tucked into the opening in the artery (Fig. 1). The purse-string suture was tied and was oversewed with two additional running silk sutures. The clamps were removed and the artery replaced in its bed. The patient noticed no recurrence of the bruit following the removal of the clamps which had been

left on for about twenty minutes with no untoward effects. A vasselinized tape was put around the internal carotid artery to allow for traction hemostasis in the event that the arterial sutures failed to hold. This was removed twenty-four hours later. The wound was closed with buried silk and with clips to the skin. The patient's condition and morale were excellent throughout.

She was sent to the x-ray department and the plates showed the silver clip to be in the right side just at the outer side of the dorsum sellae and on a level with its floor (Fig. 2).

The patient was kept in bed and strict quiet was enforced to reduce the possibility of embolism to a minimum. She complained of headache and had some emesis for two days, probably the result of the increased cerebral blood flow.

On the third day, a thrombus was palpable in the upper lid and chemosis of the conjunctiva was becoming prominent. On the sixth postoperative day a bruit was audible by the stethoscope, but the patient could not hear it and pulsation was not palpable. Thinking that the muscle embolus might have shifted, another x-ray picture was made, but the clip was reported to be in its original position. Chemosis and injection of the conjunctiva, particularly of the lower lid, increased, but yellow oxide of mercury ointment and iced compresses gave great relief. On the sixteenth day a pulsation was felt in the supra-orbital region and the chemosis began to recede. Recession was progressive and the patient felt well in every way.

On June 10, 1931, twenty-six days after the operation the conjunctiva was somewhat congested, there was moderate chemosis in the lower portion, but the pulsations were no longer palpable, and while the bruit was audible to the stethoscope, it was much less than it had been a week previously. The patient had not heard the bruit since operation.

Dr. Barney Brooks, of Nashville, Tenn., first devised this method of treating arteriovenous aneurysm, feeling that the old principle of ligation of the common or internal carotid artery proximal to the arteriovenous communication was as erroneous in theory as it was disappointing in practice. Occlusion of the fistulous opening must be secured before the lesion can be considered conquered. Dr. Brooks usually uses a long thin strip of muscle instead of a small piece, as we did.

Several other operators have used the method and the results appear to be encouraging, although the number is as yet too small to allow accurate conclusions to be drawn.

GASTROJEJUNO-COLIC FISTULA

A Report of Two Cases With Recovery

John C. Jones

Case I

A man, 45 years of age, presented himself at the Clinic on July 21, 1931, complaining of "stomach trouble." He stated that 11 years previously he had first noted epigastric, gnawing pain, which came on from one to three hours after eating. During the night he would be awakened by the same type of pain, which was always relieved by eating, by alkalies and by drinking milk. He had been on Sippey diet several times by the advice of various physicians, and six years before, he had received medical treatment for "ulcer" for one month at Lakeside Hospital. He was comfortable while under medical treatment but the pain recurred as soon as he discontinued the Sippey diet. Becoming discouraged with medical treatment he sought surgical relief and was admitted to Charity Hospital in September, 1929, where I first saw him on Dr. C. A. Hamann's service. The patient was then complaining of this same type of pain, of the "belching of considerable gas" and at times of nausea without vomiting. The preoperative diagnosis was duodenal ulcer.

He was operated upon by Dr. Hamann who made the following note: "There is a marked indurated ulcer right at the pylorus, adherent to the under surface of the liver and gall bladder. There is quite a mass, very firm to touch. No stones in the gall bladder. It was thought best not to separate it from the gall bladder and liver. One or two stitches across the pylorus were put in. A posterior short-looped gastroenterostomy was done. Appendix normal, not removed, postoperative diagnosis, duodenal ulcer."

Convalescence was uneventful, the patient was placed on a Sippey diet and left the hospital twelve days after operation.

Three months later he returned to work, having been symptom free in the interim. Soon afterwards, about nineteen months before he entered the Clinic, there was a recurrence of epigastric pain, which, as before, was relieved by eating and by alkalies. The pain was accompanied by intermittent attacks of vague, cramplike pain in the mid-lower abdominal region. These attacks lasted from a few days to a week; they usually were not relieved by eating but were somewhat relieved by the "belching of gas." The patient volunteered the information that four and one-half months after his operation an x-ray examination had revealed an ulcer at the site of the gastroenterostomy. One year previously he had vomited a considerable

amount of bright-colored blood, followed by a tarry stool. Weakness and anorexia had been progressive and he had lost 15 pounds in the past few weeks. For three weeks he had had a severe diarrhea, with several bowel movements daily, one a half-hour after each meal, and although there was no vomiting, fecal or otherwise, he had had very foul eructations. He recalled having seen undigested food in his stools but there was no melena.

The personal history was irrelevant. The physical examination gave the following findings: the patient was a short, asthenic man, weighing 125 pounds. The pulse rate was 70, the blood pressure 100–40. The teeth were dirty and carious, with pyorrhea alveolaris. There was no pathological condition of the heart or lungs; the abdomen was scaphoid in contour; there was a scar four inches long over the upper right rectus muscle; the muscles were slightly weak but no hernia was present; although there was no rigidity or spasm the patient was unable to relax the abdomen completely. Slight tenderness was present in the epigastrium and there was a feeling of resistance although no tumor masses were palpable; the liver and kidneys were not palpable, the spleen was not enlarged.

Genito-urinary, rectal and gross neurological examinations gave negative findings.

Laboratory data — Urinalysis, Kahn, and Wassermann tests gave negative findings; red blood cell count, 4,430,000, white blood cell count, 8100, hemoglobin, 94 per cent; blood sugar 112 mg. per 100 c.c.; blood urea 42, mg. per 100 c.c.; urea clearance: 95 per cent the first hour and 125 per cent the second hour.

Dr. Hartsock, of the Medical Division, made a clinical diagnosis of "gastrocolic fistula" which was confirmed by x-ray examination. The barium meal passed directly from the mid-portion of the stomach into the transverse colon. The barium enema filled the stomach through the communication with the transverse colon.

Operation was advised and the patient was admitted to the hospital July 23, 1931. He was placed on a Sippey diet, and given 2000 c.c. of 10 per cent glucose intravenously daily.

Operation, under spinal anesthesia, was performed on July 27, 1931, by T. E. Jones. A gastrojejuno-colic fistula resulting from a marginal ulcer was found at the site of the old posterior gastroenterostomy together with a separate jejunal ulcer about one and one-half centimeters in diameter on the mesenteric aspect, just opposite the stoma. The fistula was excised, the opening in the colon closed, the jejunal ulcer was resected and the distal end of the jejunum was sutured to the opening in the stomach thus forming a new gastroenterostomy. The proximal jejunum was then sutured

to the distal segment of the jejunum after an opening had been made in the latter about two inches below the gastroenterostomy, forming an end-to-side jejuno-jejunostomy. This completed the so-called "en-Y" operation of Roux. The patient was immediately given a transfusion of 500 c.c. of whole blood and returned to his room in good condition. Postoperative treatment consisted of the Alonzo-Clark routine, a subcutaneous saline infusion — 2000 c.c., once daily, and an intravenous infusion of 10 per cent glucose, 1000 c.c., twice daily. On the fifth postoperative day the patient was placed on a surgical Sippey routine. Up to this time an intranasal catheter had been left in the stomach for drainage. For the first four days the temperature was constantly above 101.3° F. having reached 104° F. the evening of the first day. However, the patient's course was practically uneventful, a normal temperature being maintained from the seventh day on. The wound healed well and on the eighth day the bowel movements were normal. The patient was discharged in good condition on the seventeenth day.

He has been on four hourly Sippey feedings and when he recently returned to the Clinic for a check-up he was symptom-free. In the three and one-half months since he left the hospital he had gained 20 pounds. A recheck of the gastrointestinal tract while revealing a rapidly emptying gastroenterostomy gave otherwise negative findings. It is impossible to predict the ultimate result in this case for not enough time has elapsed to make a definite statement regarding the prognosis. The results are satisfactory thus far.

Case II

A man, 57 years of age, came to the Clinic on June 3, 1927, complaining of "pain in the right side." He stated that he had been well up to the age of 28 when he began having intermittent pain in the right abdomen accompanied by vomiting. In 1905 the right kidney had been anchored, and the appendix and gall bladder removed. He had relief for one year only. In 1915 he was operated upon and an old duodenal ulcer was found for which a posterior gastroenterostomy was performed. Again he obtained relief for but one year. In 1921 an exploratory operation was performed, and "the redundant portion of the stomach sutured." In 1926 a stone was removed from the left ureter. There had been no recurrence of symptoms of ureteral stone.

Ever since his last operation which was performed eight months previous to his admission to the Clinic, the patient had complained of severe pain in the upper abdomen particularly on the right side, vomiting of bile and of yellow, thin material that was bitter, and no food. Vomiting gave considerable relief. The stools had been normal

in color but there had been a tendency to loose stools. This condition had been particularly aggravated by the use of alkalies which gave slight relief from the pain. There was no loss of weight.

The physical examination gave the following findings: weight 130 pounds, temperature 99.2 degrees F., pulse rate 100, blood pressure 160–110. The skin was sallow and the mucous membranes showed a suggestion of cyanosis. The upper teeth were all missing, and the remaining lower teeth were dirty. Nothing abnormal was found in the heart or lungs.

Abdominal examination revealed bilateral lumbar scars, a McBurney's scar and two right rectus scars. Tenderness was present over the upper abdomen and an indefinite mass could be palpated in the right upper quadrant. The inguinal rings were bilaterally relaxed and the prostate was slightly enlarged.

The clinical diagnosis included postoperative adhesions, dilatation of the common duct with retention of bile, relaxed inguinal rings, and hypertension.

The laboratory findings were as follows:

Urinalysis gave negative findings except for a very faint trace of albumen. Red blood cell count, 4,460,000, white blood cell count, 9550, hemoglobin 75 to 80 per cent, Kahn and Wassermann tests gave negative findings, blood sugar 112 mg. per 100 c.c. (two hours postprandial) blood urea 39 mg. per 100 c.c.

The roentgenographic findings were: Gastrointestinal series gave the following findings: nothing abnormal in the plain gall bladder plates, the duodenum was deformed by adhesions and showed slight retention. The gastroenterostomy did not function; the colon showed a constant filling defect, the lumen being narrowed in the transverse portion just under the scar of the "gall bladder lap," this was not a typical picture of carcinoma; all the abdominal anatomy was quite altered by the surgical operations that had been performed.

Nothing abnormal was found on the K.U.B. films.

The patient was seen in consultation by Drs. Crile, Lower, and Phillips, who agreed that medical treatment was indicated rather than surgery. A Sippey diet and alkaline powders were prescribed and the patient was sent home to be under the care of his home physician.

He returned to the Clinic three months later stating that he had had a persistent diarrhea for a month, with five to six stools a day. There was no blood in the stools, but considerable gas and mucus was passed and for two nights there had been incontinence of the bowels. For the past two days he had had a "griping pain" in

the lower abdomen, and a persistence of the right upper abdominal pain. He still had lost no weight.

A second x-ray examination gave the following findings: The stoma functioned normally, the stomach being empty at the end of five hours. A small portion of the barium passed through the small intestines but the greater portion passed directly into the transverse colon just distal to the hepatic flexure via a fistulous opening between the jejunum and transverse colon. The stomach was easily filled with barium by means of a barium enema. The x-ray diagnosis was gastrojejuno-colic fistula.

The patient again returned home to be under the care of his physician. He was placed on a Sippey diet, and was given large doses of bismuth, but grew progressively worse. He returned to the Clinic four months later, with the same complaints of persistently severe diarrhea, progressive anorexia, nausea, vomiting and weakness, having lost 25 pounds in weight during the four months. Surgical treatment was advised and he was admitted to the hospital on January 3, 1928.

The laboratory data were as follows: x-ray recheck of the colon showed the stomach filled by the barium enema. Red blood cell count 4,040,000, hemoglobin 60 per cent. Urinalysis gave negative findings. Fasting blood sugar 68 mg. per 100 c.c., fasting blood urea, 30 mg. per 100 c.c.

The patient was given frequent small feedings and his diet was increased; the fluid intake was kept up and as a result he was free from nausea and vomiting. On January 12th, nine days after entering the hospital he was operated upon by Dr. W. E. Lower. An old gastric resection was found. The fistula was located at the site of the posterior gastroenterostomy. The gastroenterostomy was opened, the thickened portion of the stomach about it resected, and the opening in the stomach closed. A new posterior gastroenterostomy was made and about three inches of the transverse colon, including the fistulous tract, was resected. An end-to-end anastomosis of the transverse colon completed the operation. A transfusion of 500 c.c. of whole blood was given immediately after the operation.

The patient was placed on the Alonzo-Clark routine for four days, after which the fluid intake was gradually increased. Each day saline was given by hypodermoclysis, and glucose was administered intravenously. On the seventh day, however, an attack of coughing caused the abdominal wound to become separated, and secondary suturing was necessary. On the same day the patient received a second blood transfusion and his course was uneventful

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thereafter; the wound granulated well and the patient left the hospital on the twenty-third postoperative day.

A Sippey regimen with alkaline powders was prescribed. Convalescence was rapid at home; the patient gained twenty-five pounds in two weeks, and 42 pounds in six months.

The patient returned to the Clinic about two months before this report, presenting no symptoms referable to the gastrointestinal tract but complaining of symptoms of hypertension which had lately developed.

REVIEW OF THE LITERATURE

Previous to 1903 about 70 cases of gastrocolic fistula had been reported in the literature, all of which were the result of carcinoma of the stomach or colon. In 1903 Czerny[1] reported the first case of gastrocolic fistula following gastroenterostomy and since then 124 similar cases have been reported. In all, there have been reported over 250 cases of all types of gastrocolic fistula resulting from organic diseases of the stomach and colon, such as carcinoma, trauma, etc. The incidence of the type due to carcinoma is increasing with the increasing frequency of operations.

In 1924 Verbrugge,[2] of the Mayo Clinic, in a study of all cases of gastro-colic fistula, collected 202 cases from the literature, seven of these being from the Mayo Clinic. He added 14 more cases bringing the total to 216. Of the 21 cases reported from the Mayo Clinic, two resulted from carcinoma of the transverse colon, and 19 from jejunal ulcers following gastroenterostomy; seven of these cases were not diagnosed either clinically or by x-ray, 14 cases were diagnosed by x-ray and 13 cases were diagnosed clinically, one being doubtful. Of the 216 cases reviewed by Verbrugge, 95 cases resulted from posterior gastroenterostomy, and 121 cases from organic lesions of the stomach and colon, chiefly carcinoma.

In May, 1931, Wiese[3] reviewed 119 cases in which a gastrocolic fistula had followed gastroenterostomy and added two of his own; however, in his report, he did not include one case reported by Gatewood[4] and two cases reported by Hübscher.[5] In 1912 Haudek[6] made the first roentgenologic diagnosis of gastrocolic fistula but Burnham[7] in 1917 was the first to report a case of gastro-colic fistula diagnosed by the x-ray. In all cases reported since 1924, including the two cases reported herein, the condition has been either diagnosed or confirmed by x-ray.

Loewy[8] in a series of 63 cases, reported a mortality of 27 per cent, and 62 per cent cures, with definite recurrences, however, in 11.1 per cent.

Etiology — Gastro-colic fistulae are due to the perforation of gastrojejunal ulcers. This was found to be the case in from two to five per cent of the cases of gastrojejunal ulcer found in the United States. The Mayo Clinic reports an incidence of 11.36 per cent. In similar analyses, Bolton and Trotter[9] report an incidence of 10 per cent, and Lion and Moreau[10] report an incidence of 12 per cent. In the German literature the incidence is placed somewhere between 5 and 10 per cent.

In 1929 Katzoglu[11] collected from the literature 117 cases of gastrojejuno-colic fistula following gastroenterostomy and added two of his own. He suggests the restoration of normal channels as a means of lowering the mortality which is given as 20 per cent.

The factors which account for the development of gastro-jejuno-colic fistulae are the same as those which account for the origin of the marginal ulcer, namely, the following:

1. Carelessness in postoperative management.

2. Causes similar to those of the original peptic ulcer.

3. The use of unabsorbable sutures. However, several authors deny this.

4. Trauma of the mucosa at operation.

5. Position and inadequate patency of the stoma.

Symptomatology

The symptoms of gastro-colic fistula vary in degree and in accordance with the size and directness of the fistula. The most constant and frequent symptom, and the first to appear, is the eructation of foul gas.

Diarrhea is usually present and is an important factor in the diagnosis. This symptom was absent, however, in two cases reported by Monroe and Emery.[12]

Pain is a variable symptom. It is sometimes marked, as the result of localized peritonitis, or it may be almost absent; in fact, the pain from the ulcer not uncommonly disappears after the development of the fistula.

Loss of weight is usually marked, with a correspondingly increasing weakness. The appetite may remain good.

Vomiting may occur. Frequently when the diarrhea is checked fecal vomiting results. The vomitus may not be fecal, however. Anemia is present with little or no apparent loss of blood.

Several cases have been reported in which marked edema was present. This is undoubtedly due to a nutritional disturbance either from lack of food, or from non-absorption due to the gastrointestinal disturbance. Even with an adequate mixed diet, as long

as there is a "short circuiting of the small intestine," the food is not absorbed and consequently, there is a presistent edema. No apparent cause has been found for the edema in the cases in which autopsy has been done, but the condition is probably due to a disturbance of the blood protein.

The physical examination usually reveals localized tenderness and a palpable mass in the region of the fistula, anemia and emaciation, and sometimes edema.

The *diagnosis* is usually made from the history. It is extremely important to make an x-ray examination in each case in which diarrhea develops following a posterior gastroenterostomy. The vomitus should be examined as well as the stools, and although a fluoroscopic examination of the stomach is of diagnostic value it is easier to distinguish the fistula by means of a barium enema. Every case of gastrocolic fistula can be diagnosed by x-ray examination. Dyes may be used and the excretion of substances given by mouth may be timed. There is no record of any cases in which spontaneous healing occurred, many cases having gone on for long periods without operation.

TREATMENT

Once the diagnosis has been established, operation is indicated as soon as the condition of the patient warrants it. Blood transfusions without limit should be employed in the far advanced cases and in any case in which there is a disturbance of serum protein fractions. The type of operation depends entirely on what is found when the abdomen is opened. Balfour recommends pylorisection to prevent recurrence.

Good postoperative management is most essential. To obtain the best results, accurate dietary management should be instituted.

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